Acta
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SUPPLEMENT 301

Inner Ear Studies

from

The Ear Nose and Throat Department
The University of Uppsala, Sweden

and

The Bioacoustics Research Laboratory
Department of Electrical Engineering
University of Illinois, Urbana, USA

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(Head: H. Engström, M.D.)[A]

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(Director: H. W. Ades, Ph.D.)[B]

CONTENTS

Acknowledgements

The authors would like to acknowledge the cooperation of Professor B Vincent Hall, Head of the Center for Electron Microscopy University of Illinois, Urbana An extensive portion of the technical management in Uppsala was handled by B Engstrom, Res. Eng., by G Rajamäki, sectioning, and by L. Svedjeblick, photography Their assistance has been of great importance for the completion of the publications. We also gratefully acknowledge the assistance of Mrs U Wikberg, Secretary

A. Studies 1–4 have been supported by the Physiological Psychology Branch Office of Naval Research, Washington, D C. under Contract N00014-69-C-0334 by the National Aeronautics and Space Administration, NASA Grant NGR 52-028-003 by the Swedish Medical Research Council, Projects No B71 12X 3156-01A and B72 12X 3156-02B

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Scanning Electron Microscopy of the Normal and Pathologically Altered Organ of Corti

by Goran Bredberg,[1] Harlow W Ades[2] and Hans Engström[1]

INTRODUCTION

The authors have published a series of articles over a period of several years dealing with the morphology of the inner ear of animals and man. Many of those have been devoted to a systematic mapping of the sensory cells and nerve elements of normal and pathologically altered cochlear and vestibular epithelia. They were predicated initially on the idea of portraying properly the cell destruction caused by noise and ototoxic antibiotics. It was considered further that they would gain by the application of electron microscopic techniques Transmission electron microscopy while yielding illuminating insights on certain qualitative factors, did not give a quantitative estimate of the sensory cell population in normal or damaged cochleas, as it was known it would not. This left a need for a method of quantitating cells throughout the sensory organ which in turn led to the development of the surface specimen method by which each sensory cell of the organ of Corti can be examined *in situ* and the entire organ mapped accordingly by light/phase contrast microscopy

During the further development of the surface specimen method and its application to problems of noise exposure, the technique of scanning electron microscopy became available to us, and has proven to enjoy certain advantages over both light/phase contrast microscopy and transmission electron microscopy though it does not supplant either What it does in part is to bridge the wide gap between light microscopy and transmission electron microscopy It is an additional adjunct to the study of the inner ear and only by the judicious combinations of methods and their convergence on the same problems can progress be firmly made. Thus, conventional transmission electron microscopy has been used widely and has contributed greatly to the knowledge of inner ear morphology Likewise, light/phase contrast microscopy has clarified, both before and since, many interesting aspects of the morphology of both cochlear and vestibular portions *of the* inner ear Scanning electron microscopy has

[1] Dept of Otolaryngology University of Uppsala, Sweden
[2] Depts of Physiology and Electrical Engineering, Bioacoustics Research Laboratory University of Illinois, Urbana, Illinois, USA.

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A

TM

IHC

BM

Fig. 1. In Fig. 1A the organ of Corti of a cat is seen in a conventional midmodiolar section. Both sensory cells and supporting elements are easily recognized. In Fig. 1B a corresponding specimen from a guinea pig has been photographed in the scanning electron microscope (SEM). The inner hair cell (*IHC*) and three rows of outer hair cells (1 → 3) are seen. Basilar membrane (*BM*). Tectorial membrane (*TM*). (A) ×370, (B) ×375.

already had a considerable impact on this research illuminating structures which were previously seen dimly or not at all. It does so by showing true three dimensional pictures with a great depth of field and good resolution. It has added a new dimension to cochlear morphology which while mainly in the realm of surface features, is applicable to a more limited degree to subsurface structures as well. It has proved to have great advantage in visualizing features which have hitherto been seen in three-dimensional view only through re constructions

In recent years a number of studies have accumulated relating to scanning electron microscopy on biological specimens. Biological applications have been reviewed by Hayes et al (1966) Hayes & Pease (1968) Barber & Boyde (1968) and Small & Marszalek (1969) The inner ear was first studied with the scanning microscope by Barber & Boyde (1968) in their study of ciliated epithelia. Lim & Lane (1969 *b* *c*) Lindeman (1970) and Kellerhals et al. (1970) studied the vestibular epithelia The cochlea was studied by Lim & Lane (1969 *a* *c*) Bredberg et al (1970) Engström et al (1970) Marovitz et al. (1970) Thalmann et al. (1970) and Lundquist et al. (1971) The earlier studies on the inner ear were accomplished with air dried specimens (Barber & Boyde 1968 Lim & Lane 1969 *a* *b* *c*) but they showed many artefacts due to shrinkage and compres sion *Since then the techniques of preparation have improved greatly and* there are a number of papers in which they have been discussed (Small & Marszalek 1969 Bredberg et al. 1970 Marovitz et al. 1970)

Most of the pictures presented in this paper represent some aspect of the normal morphology of the organ of Corti. They illustrate the three-dimensional structure in a new way that was made possible by the scanning electron microscope There are a few figures, mainly transmission electron micrographs, which show the interrelationship and interdependence of transmission electron microscopy and scanning electron microscopy or illustrate in a different way what is seen in a scanning picture There are some few figures which are taken from pathological cochleas, or fetal cochleas, and are included to provide illustrations of a few things that can be done with scanning electron microscopy and to indicate a few obvious areas of future research This presentation in no way claims to give a complete picture of the morphology of the organ of Corti For detailed information the reader is referred to Engström et al (1966) Spoendlin (1966, 1970) Iurato (1967) Bredberg (1968) Engstrom & Ades (1971)

METHODS

A specimen which is to be studied under the scanning electron microscope must fulfill certain minimal requirements

1 *Its size must be small* enough to allow it to be mounted in the specimen chamber The specimen normally up to 10 mm maximum diameter is glued to a metallic holder although there is now a stage and specimen holder that can accommodate one of five times that size (however it should be kept in mind

that a specimen of this size cannot be studied as a whole, but only as a series of parts)

2. It must tolerate the high vacuum of the microscope. When scanning electron microscopy was first developed, its use was confined to the study of hard materials which met the requirement of tolerance to high vacuum. Difficulties arose as investigators sampled biological specimens which consist mostly of water because this component had to be removed without significantly altering the shape of the remaining structure. Freeze drying techniques can generally accomplish this now. The most comprehensive paper on the preparation of animal tissues for scanning electron microscopy was written by Boyde & Wood (1969) in which they surveyed the problems encountered in the preparation of biological specimens, offered advice, and gave a number of technical details on how to manage the preparation.

3. It must be electrically conducting in order to remove electrons bombarding it. The electrons reaching the specimen must be conducted away or the specimen will be charged by the electron beam, which will disturb the secondary electrons or the electron beam itself. If the specimen is metallic, this problem is automatically solved but for non-metallic specimens, as we were using, a thin layer of conducting material must be applied. It must have good conducting qualities and should be a substance of high atomic number that will give a high emission of secondary electrons, thus giving a good signal. Gold or a combination of gold and palladium are commonly used however copper aluminum, and carbon may be used for special purposes.

The experimental animals (guinea pig, cat, monkey and chinchilla) were anesthetized with Nembutal before decapitation and removal of temporal bones. The perilymphatic cochlear spaces were perfused with a fixative. One of three fixatives was used. (1) A modification of Parducz (1966) consisting of 6 parts 2% phosphate buffered osmium tetroxide (Millonig, 1961) and 1 part saturated $HgCl_2$. (2) 1.5% veronal buffered osmium tetroxide solution, (3) 1.5% veronal buffered glutaraldehyde.

The human cochleas were fixed by injecting the fixative selected into the perilymphatic spaces 2–6 hours post-mortem and leaving it in the labyrinth until the temporal bones were removed at autopsy (method described in detail by Bredberg, 1968). The time of fixation with the Parducz fixative and with the buffered osmium tetroxide was 1–2 hours, and with glutaraldehyde 2–4 hours. After glutaraldehyde fixation, the specimens were kept in 1.5% veronal buffered OsO_4 for hours. Fixation of the human cochleas was subject to much more variation since it was not always possible to get access to the temporal bones at the desired time of fixation, hence the time could be up to 24–48 hours.

After fixation, the specimens were rinsed in glass-distilled water and dissected under a preparation microscope. In the guinea pig, the bony capsule around the cochlea was easily opened with watchmaker's forceps, whereas in the cat, the chinchilla and the monkey, in order to gain access to the organ

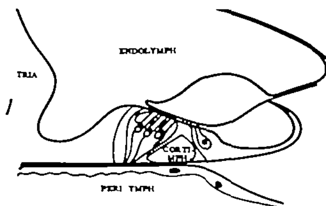


Fig 2 Schematic drawing of the organ of Corti to show the fluid spaces where perilymph, endolymph and possibly a third fluid, cortilymph, are found.

Fig 3 In 3 A we can see the surface of the organ of Corti of a *guinea pig. The hair bundles have* been visualized by the zinc-iodide stain of Maillet In 3 B a corresponding phase contrast photo-micrograph surface specimen technique The inner hair cells (*IHC*), the heads of the pillars (*P*) and three rows of *outer hair cells (1 3) (A) 150*× (B) × 275

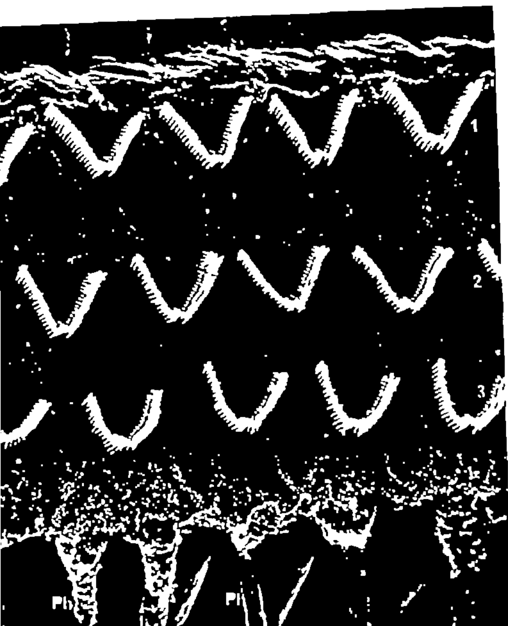


Fig. 5. Three rows of outer hair cells (1, 2, 3) and surrounding supporting elements. The W-form of the hairs is very clear. *Ph* indicates phalangeal processes of the third row of Deiters' cells. On the phalangeal plates, inbetween the sensory cells microvilli are seen. × 5 900.

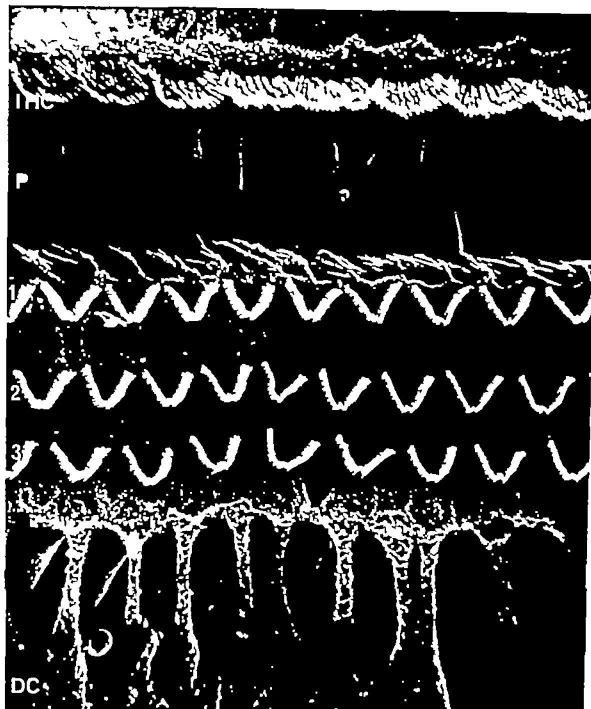


Fig. 4. The upper surface of the organ of Corti of a cat as seen in the SEM. The inner hair cells (*IHC*), the pillar heads (*P*) and three rows of outer hair cells (1 → 3). The phalangeal processes of the third row of Deiters cell (*DC*) are also seen by virtue of the fact that the Hensen cells have been removed. ×90

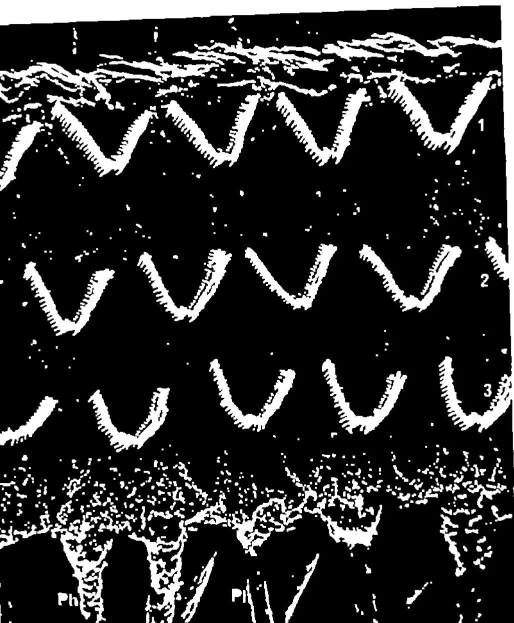


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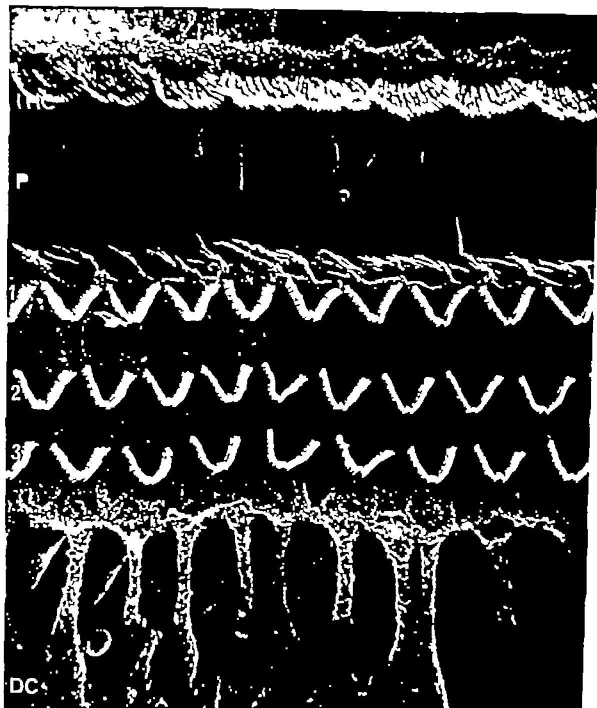


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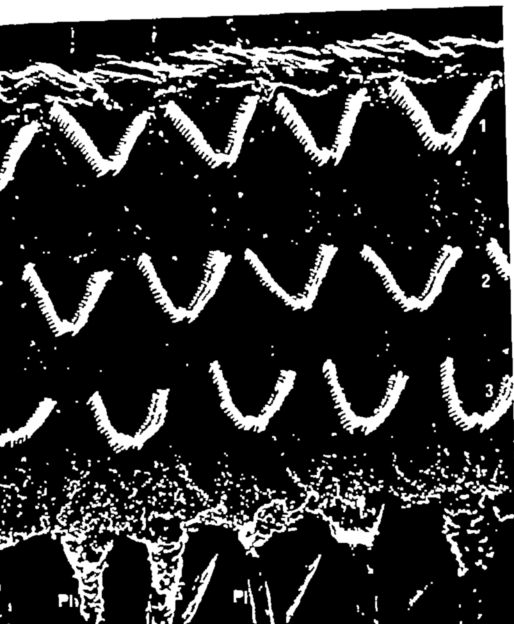


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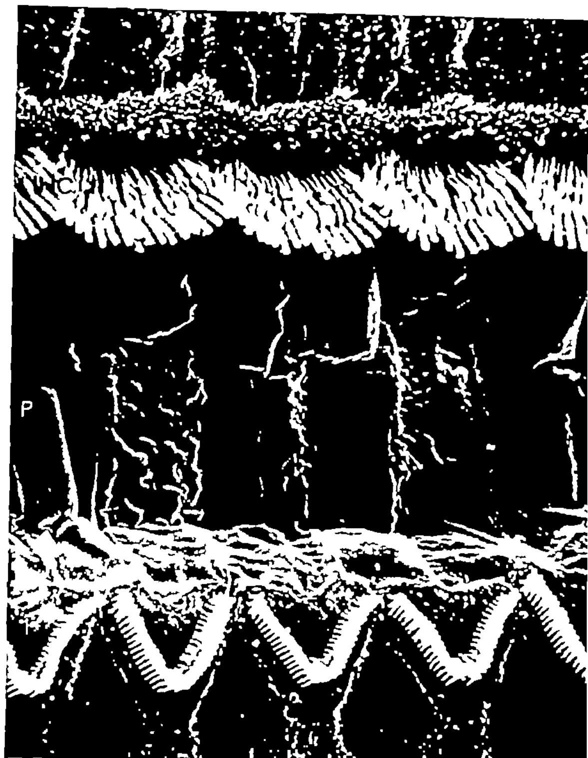


Fig 6 In this micrograph one row of inner hair cells (*IHC*) and the first row of outer hair cells (1) surround the pillar region (*P*) Th h irs on the inner hair cell h ve a varying length This is true also for the outer ha cells but less prominent Above the inner hair cells one row of cells with numerous m cr vill ca be seen Cat middle coil 6 600

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of Corti the bony capsule had to be thinned down with diamond dental burrs before it was opened. The method of dissection is essentially the same as de scribed by Engström et al (1966) and Bredberg (1968)

The bony capsule was opened and the spiral ligament was removed with



Fig. 7. The tunnel region surrounded by inner (*IP*) and outer (*OP*) pillars. Through the tunnel, above the basilar membrane (*BM*) several radiating tunnel fibres (*RTF*) are seen. Three rows of outer hair cells (1 ... 3) are also seen. Cat. 1 800

great care. The osseous spiral lamina was dissected free with the organ of Corti in half coils or smaller segments, and placed in a jar of glass-distilled water. At this stage the tectorial membrane covering the surface of the organ of Corti was removed and discarded unless it was to be studied *in situ* in a particular specimen. The dissection was carried out further in some specimens to include the modiolus and modiolar aspect of the organ of Corti.

The specimens were placed in a drop of glass-distilled water on a thin aluminum plate. They were initially frozen by rapidly dipping the plate into isopentane which was kept just above its freezing point at −150° to −160 C by means of liquid nitrogen. In some cases the specimens were dipped into propane kept at −150 to −180 C. The aluminum plate with the frozen specimen was placed on a copper block, cooled in liquid nitrogen and transferred to the Edwards Pearse tissue dryer where the freeze sublimation occurred

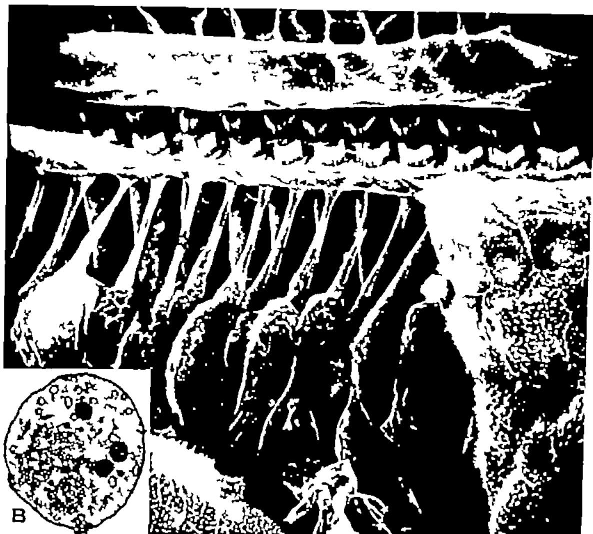


Fig 10 (A) The organ of Corti seen from the Hensen cell region towards the modiolus. *Above the organ of Corti the tectorial membrane (TM) is seen. It has become slightly* elevated from the hairs on the hair cells. The third row of Deiters cells send thin (star) phalangeal processes towards the surface. One phalangeal process is seen in *B* under the *transmission* electron microscope. *(A)* 1 650· (B) ×6 00

NORMAL STRUCTURE OF THE ORGAN OF CORTI AND ITS APPEARANCE IN THE SCANNING ELECTRON MICROSCOPE (SEM)

The sensory epithelium of the cochlea (the organ of *Corti or the spiral organ)* is attached to the basilar membrane It consists of an epithelial ridge about *100 μ in thickness which runs throughout the entire length of the* cochlear duct. The length of the organ of Corti varies from one species to another as does the size and the shape of the cochlea In man the average length is 34 mm (Bredberg 1968) in the cat, 24 6 mm (Bredberg & Ades, unpublished data) in the guinea pig, 20 3 mm (Stockwell et al 1969) in the chinchilla, 18 4 mm (Bredberg *unpublished data) in the squirrel monkey* 20 7 mm (Hunter Duvar 1971)

The structure of the organ of Corti consists of a complex of supporting

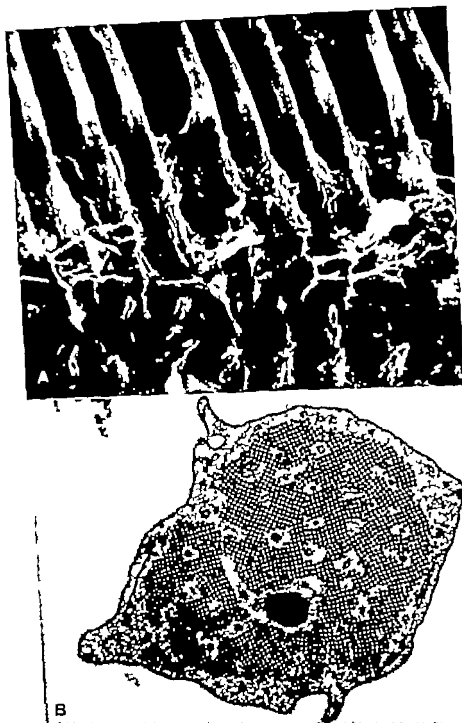


Fig. 11. In A the basal portion of several outer pillars are seen in SEM. In B corresponding pillar is seen in transmission electron microscopy. The pillar contains approximately 2 500 tubelike tonofibrils and interspersed between these an even higher number of very thin solid fibrils. (A) 2 500 (B) 34 500



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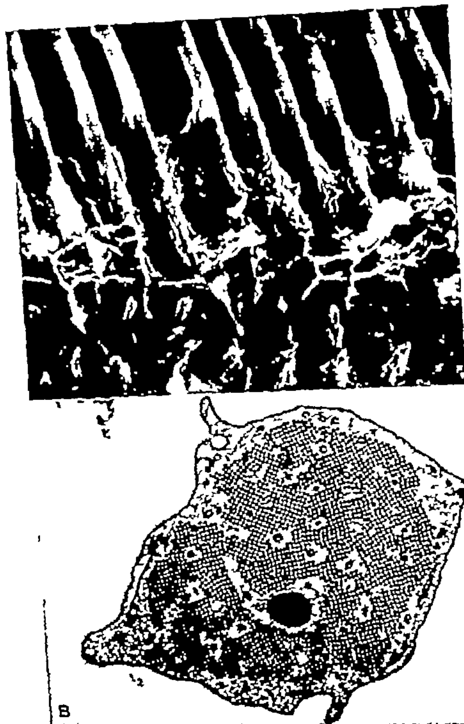


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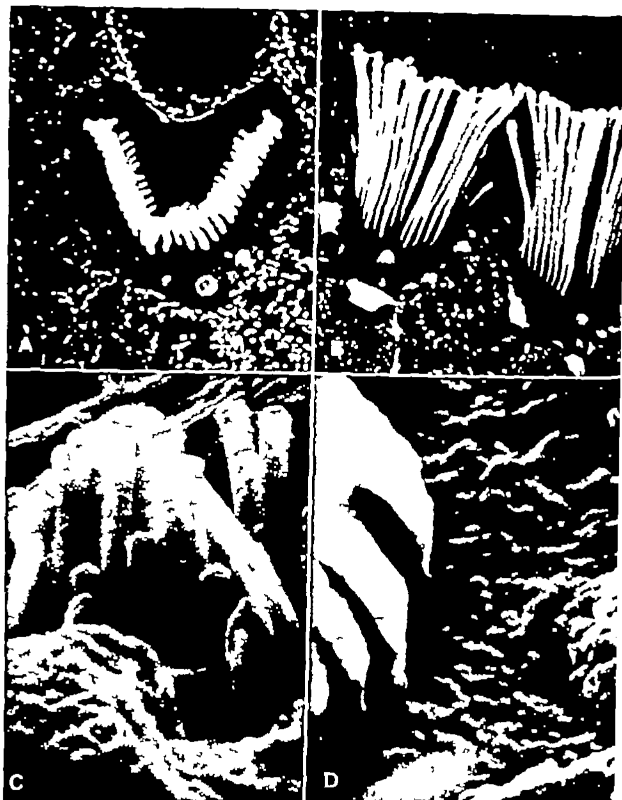


Fig. 12. Four different views on hair bundles on outer hair cells. In A from a cat, in *B* from a squirrel monkey, in C from man. In D guinea pig, the arrow points to the basal body at the surface. (A) × 10 400, (B) × 7 800, (C) × 15 700, (D) × 40 000.

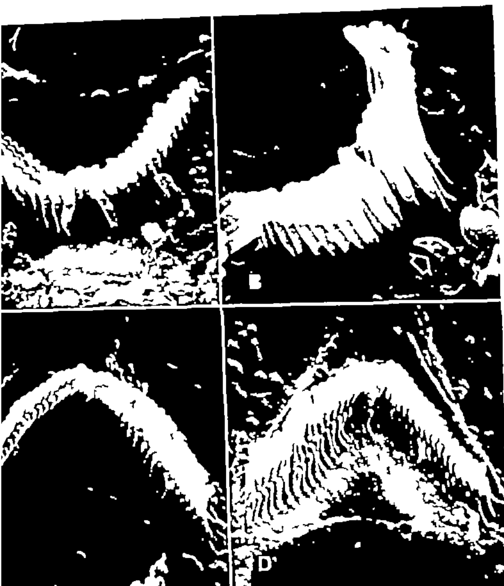


Fig 13 Four different views of the hairs on outer hair cells of *Macaca fascicularis* as seen in the SEM In B the white arrow indicates a small rest of a kinocilium (A) 14 500, (B) 18 300, (C) 15 200 (D) 14 500



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Fig 15 Hairs on an inner hair cell showing different lengths Some of the hairs have a flattened tip (star) This is very often seen and it has been observed also in sectioned material. Note the interconnections between the hairs See page 40 for a discussion of this finding Cat basal coil 23 000

cells and hair cells or receptor cells The supporting cells are slender and they extend from the basilar membrane to the surface of the epithelium forming a firm but flexible framework (Figs. 1 7 10 and 11). At the surface in conjunction with the receptor cells, they form the rigid reticular membrane The receptor cells, which are assumed to function as transducers converting sound energy to electrical events, are suspended in this membrane in spirally running rows They do not reach the basilar membrane (Figs 1 2, and 7)

The tunnel of Corti is a conspicuous feature in a radial section of the organ of Corti (Figs 1 and 7), as are the pillar cells which bound it. Close to the inner pillar (medially), the inner hair cells are seen. They are bounded laterally by the head of the inner pillar cell, and are surrounded the rest of the way by inner phalangeal cells and border cells. The outer hair cells form three rows (up to five rows in human) lateral to the tunnel and to the outer pillar heads. They are bordered on all sides by the outer phalangeal, or Deiters cells. The outermost portion of the acoustic papilla is formed by Hensen cells.

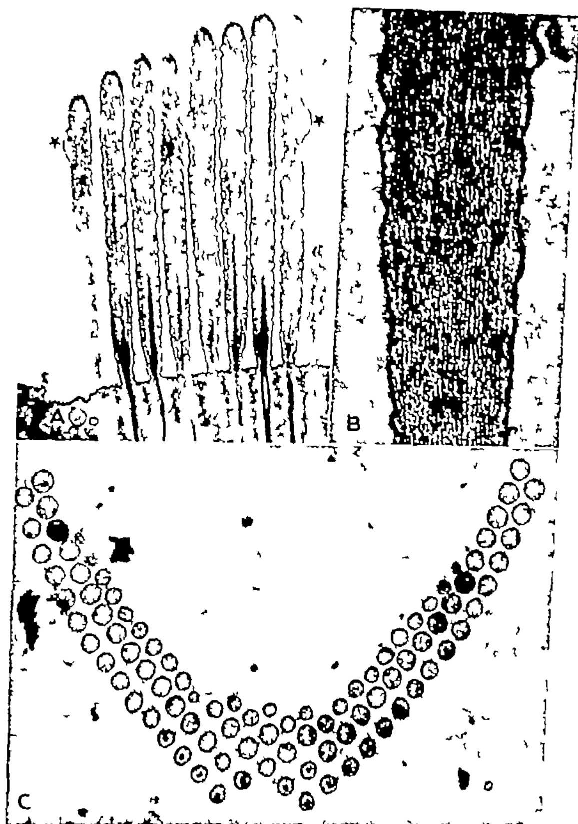


Fig 14 Structure of the stereocilia on outer hair cells In A several hairs are sectioned longitudinally and a central core and a cylindrical rootlet is seen in each hair Observe also the irregularities on some of the hairs (stars). These are found in normal animals but increase in animals exposed to noise In B the longitudinal arrangement of the hair structure can be seen In C the typical W form of the ha rs on one cell (A) 17 400 (B) 101 000 (C) 17 00



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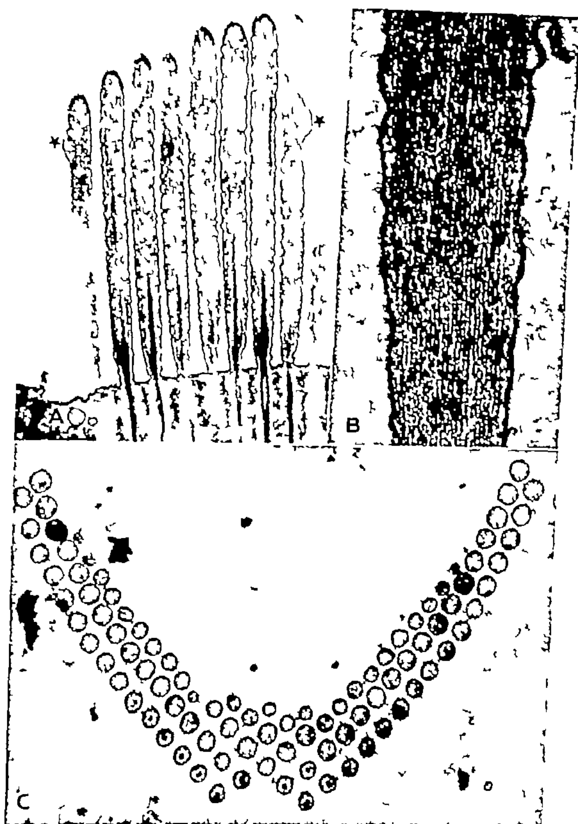
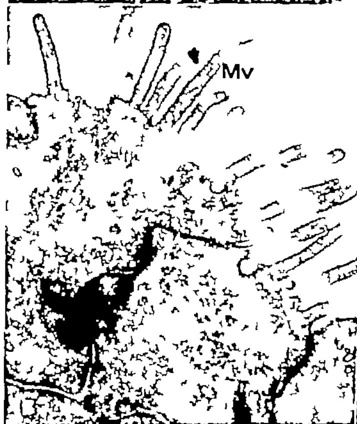


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Fig 17 The organ of Corti of human embryo showing hair bundles on the sensory cells. In each bundle there is one large kinocilium (arrow) protruding above the stereocilia. In-between the sensory cells microvilli can be seen. They are rather long t this age. SEM. 17 700

Fig 16 In A the SEM show some inner hair cells (*IHC*), some pillar heads (*P*) and cells ucally of the inner hair cells. The first group of cells are richly provided with microvilli (*MV*). These are seen in detail under the transmission electron microscope in B. On all the other supporting cells small amount of microvilli can also be seen. In C the transmission electron microscope show microvilli on some Hensen cells. (A) 3 500· (B) 37 000 (C) 35 000


Mv

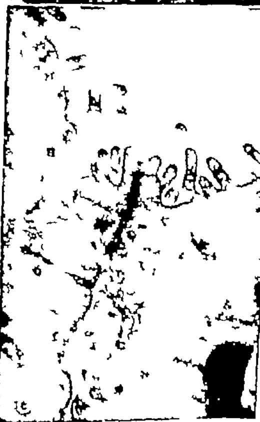




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Fig. 18. (A) Stereocilia and one kinocilium (KC) on an outer hair cell from a human fetus, age three months. The kinocilium is seen to protrude above the stereocilia. (B) The kinocilia usually disappear with increasing age. In this specimen from Macaca fascicularis, about four years old, a vestigial remnant is seen. Similar remnants were found on about one third of th outer hair cells at about one coil from base (A) 7 600· (B) 51 000

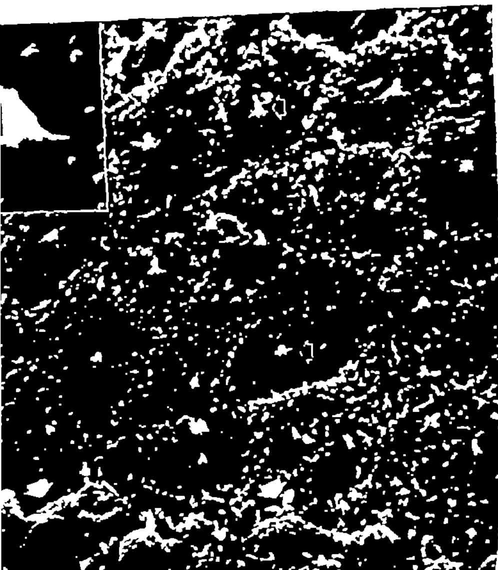


Fig 19 The organ of Corti from a human fetus with some outer hair cells (white arrows) and many Hensen cells (open arrows) The open arrows also show how all the supporting cells are provided with one kinocilium (seen in detail in *B*) *This kinocilium is here beginning* to disappear and in the adult there is *generally only a basal body or* a very rudimentary cilium left SEM (A) 6 850 (B) 34 500



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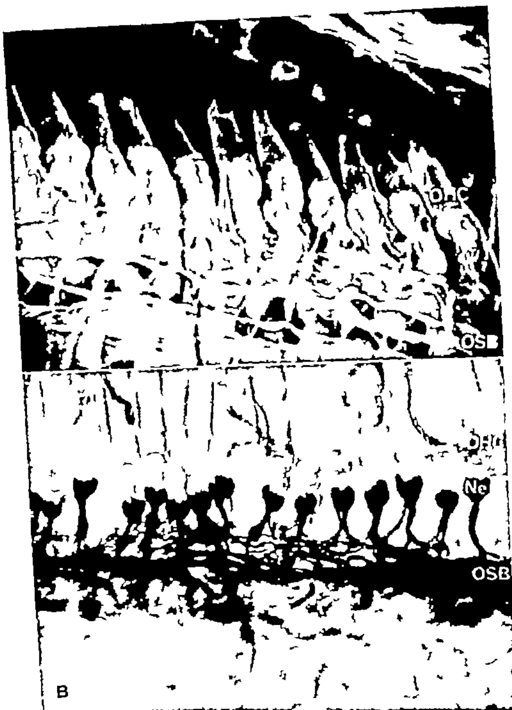


Fig. 21. In A the organ of Corti has been opened and several outer hair cells (*OHC*) are seen from below. At their bases nerve endings (*Ne*) and further down nerve fibres belonging to the outer spiral bundles (*OSB*). SEM, ×2 000. In B corresponding light microscopic picture of a Maillet stained organ of Corti. The black fibres and condensations are nerve fibres and nerve endings ×930.

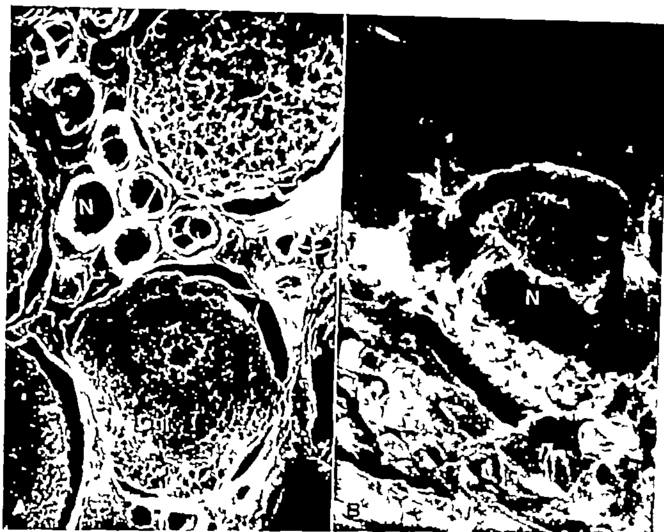


Fig 20 In these two specimens a fracture has been made through the spiral ganglion (*A*) and the spiral osseous lamina (*B*) In the ganglion cells (*Gcl*) the nucleus and the nucleolus are seen. The empty appearance of the nerve fibers (*N*) and the spongy structure of the ganglion cells are due to artefacts. In *B* the bundle of nerve fibers (N) is surrounded by bone. (A) ×4 500· (B) 800

The space between the first row of outer hair cells and the outer pillar cells (Nuel's space) is one of the intercellular spaces, all of which including the tunnel of Corti communicate freely with one another They are sealed off from the outside by the reticular membrane, Hensen's cells, the basilar membrane and the border cells (medially) As is evident from the scanning electron micrographs (Figs. 1 B 7 8 and 10) these spaces are, in fact one continuous space It is only in a conventional radial section (Fig 1 A) that it appears to be divided into several compartments. This space is filled with a fluid, the corti lymph (Engström 1960) and thus, the hair cells are bathed in this fluid.

Each outer hair cell is suspended from the reticular lamina and is supported by one Deiters cell. The phalangeal process extending from each Deiters cell to the surface of the organ of Corti forms a process, the phalangeal plate, between two sensory cells (Figs. 4 9 and 10) The phalangeal process is not associated with the same hair cell which is supported by its cell body beneath.

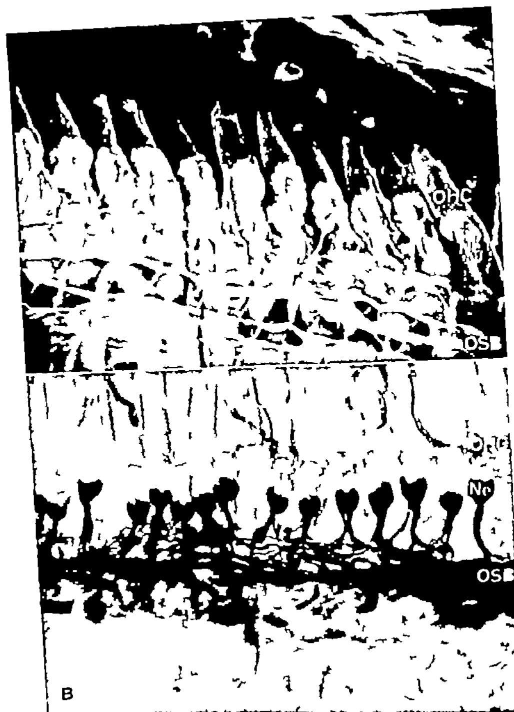


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Fig 22 Sections through a first row outer hair cell from a guinea pig as seen in the transmission electron microscope Around the base of the outer hair cell (*OHC*) with its nucleus (*Nu*) some small afferent endings (*Ne 1*) and several large granulated endings (*Ne 2*) × 1_700.



Fig. 23. Nerve endings (*N*), according to their size and form of efferent nature around the base of an outer hair cell (*OHC*). The phalangeal processes (*Ph*) of two Deiters' cells can also be seen. SEM × 13 500.



Fig 22 Sections through a first row outer hair cell from a guinea pig as seen in the transmission electron microscope. Around the base of the outer hair cell (*OHC*) with its nucleus (*Nu*) some small afferent endings (*Ne 1*) and several large granulated endings (*Ne 2*) × 12 700


TE
B



Fig 24 Four outer hair cells (*OHC*) with small nerve endings at their bases. This micrograph shows how it is possible to turn a specimen in different ways to observe different portions Black arrow indicates upper end of the sensory cell. SEM ×4 400

Fig 25 In A and B the spiral tunnel bundle (*STB*) can b seen These micrographs indicate that it is possible to fracture the organ of Corti and study some of the components in detail Compare also Fig. 26 A star in 25 A indicates hairs on inner hair cells. SEM (A) 1 840· (B) ×1 630

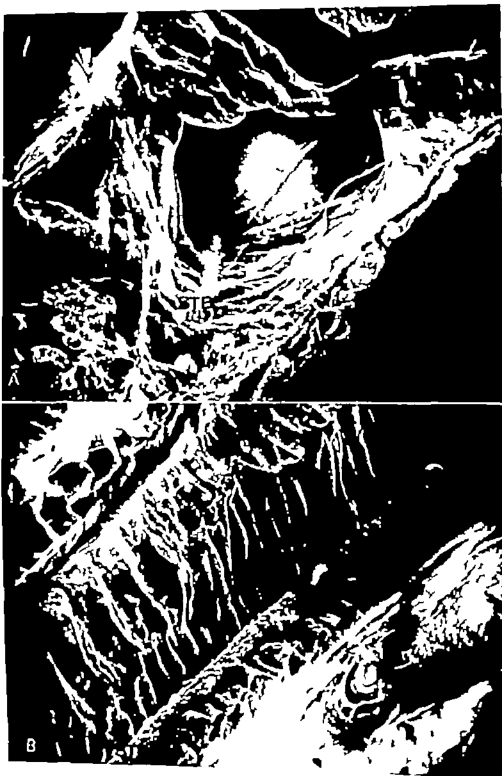

TE
A
B



Fig 24 Four outer hair cells (*OHC*) with small nerve endings at their bases. This micrograph shows how it is possible to turn a specimen in different ways to observe different portions. Black arrow indicates upper end of the sensory cell SEM 4 400

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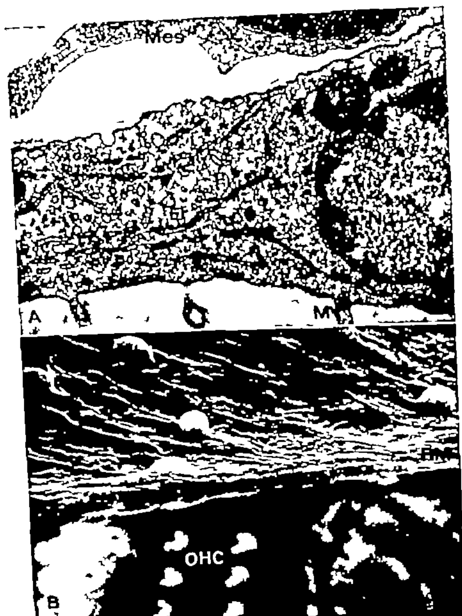
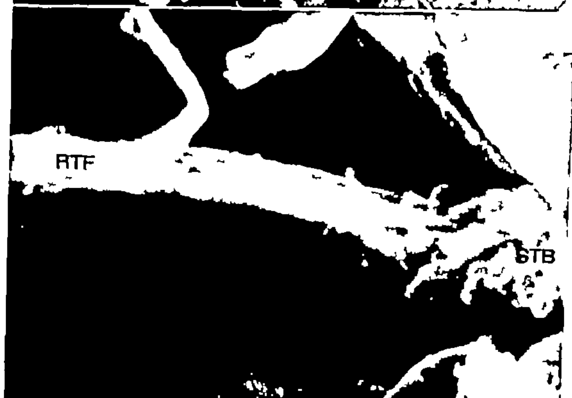


Fig 27 In B the Reissner membrane (*RM*) can be seen over the outer hair cells (*OHC*). This membrane consists of two layers of cells seen in A. The layer turned to the cochlear duct is provided with microvilli (*MV*), they have rich endoplasmatic reticulum (*Er*) with ribosomes in moderate amount. Some mitochondria (*M*) are also found. These cells show indications of micropinocytosis. The mesothelial cells (*Mes*) are in B bulging at their nuclei. They are rather rich in ribosomes. (A) × 41 000, (B) × 1 830.

Fig 6 (A) The spiral tunnel bundle (*STB*), the inner spiral bundle (*ISB*) and several radiating tunnel fibres (*RTF*) from an opened organ of Corti. In B the corresponding components can be seen at higher magnification. Observe the swellings on the spiral tunnel bundle (*STB*). They correspond to the beads containing densely packed synaptic vesicles. SEM. (A) × 3 400 (B) × 12 200.


RTF
STB

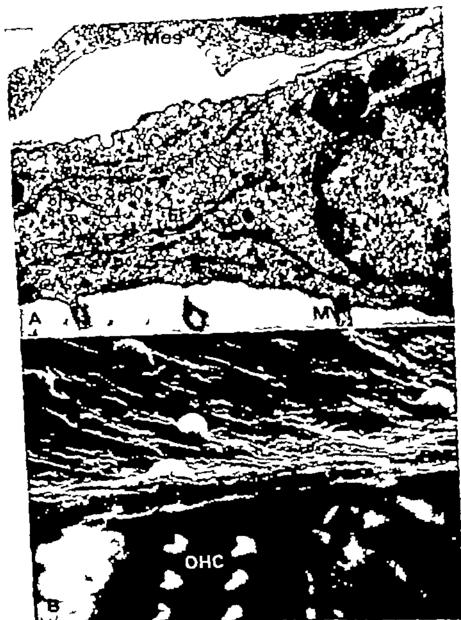


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Fig. 28. Cells of the tympanic cover layer: mesothelial cells below the basilar membrane. Note the parallel arrangement of their long processes. SEM × 2 400.

Rather there is a shift apically so that the phalangeal process helps to suspend the apical side of the hair cell adjacent to the one whose base rests on the Deiters cell itself (Figs. 4 9 and 10).

The surface of the organ of Corti is covered by a jelly-like filamentous structure the tectorial membrane which, originating from the spiral limbus, extends over the hair cells and as far as the Hensen cells (Fig 1). The longest hairs on each outer hair cell are in contact with the membrane (Kimura, 1966 Spoendlin, 1966) The free border of the tectorial membrane is fringed to form a marginal network which is in contact with the Hensen cells according to de Vries (1949) and Tonndorf et al. (1962) Lindeman et al. (1971) described a contact between the marginal fringe and the phalangeal processes of the third row of Deiters cells in kittens.

The hair cells are disposed in a highly characteristic pattern, as was recognized and illustrated in the second half of the 19th century by Retzius (1884) In most of the mammals studied, with the exception of man, the outer hair cells form three regular rows throughout the cochlea with occasional extra cells appearing in the second or third row and more rarely in the first row In man there are often four rows in the middle coil and five in the apical coil. The three rows of outer hair cells are situated lateral to the tunnel and separated from the one row of inner hair cells by the pillar cells, which also may have occasional extra cells (Figs. 1 A, 1 B, 3 and 4)

The upper surfaces of the sensory cells are suspended in the reticular lamina. The cuticular area of the upper surface of each cell is provided with sensory hairs or stereocilia which are arranged in a W-formation with the base of each W directed laterally (Figs. 5 12, 13 a and 14). The open angle of the W is wide at the base of the cochlea, and gradually diminishes toward the apex There are two other gradual changes which occur from the base to the apex of the cochlea, one being that the cuticular surfaces of the hair cells are kidney-shaped at the base, and become more oval at the apex, the other that the stereocilia increase in length. On each outer hair cell the stereocilia occur in three or more parallel rows of differing length. The outermost row is always composed of the longest hairs and the length decreases sharply in each succeeding row This is strikingly illustrated in certain of the scanning pictures, namely Figures 5 12 and 13

The inner hair cells differ conspicuously from the outer in that the W arrangement of the hairs is much less pronounced, the angle of the arms of the W being much more open than on the outer hair cells even at the base of the cochlea (Fig. 6). It approaches, but does not quite reach, 180 on the inner hair cells. The arrangement of the stereocilia in rows is very apparent, the longest again being on the outside with successively shorter hairs on the remaining rows There are more rows of hairs on the cells of the basal than on those of the apical coil (Figs. 15 and 16). The hairs of the innermost row are very short, becoming almost indistinguishable from the microvilli. In our study of the cat by scanning electron microscopy the tips of the stereocilia

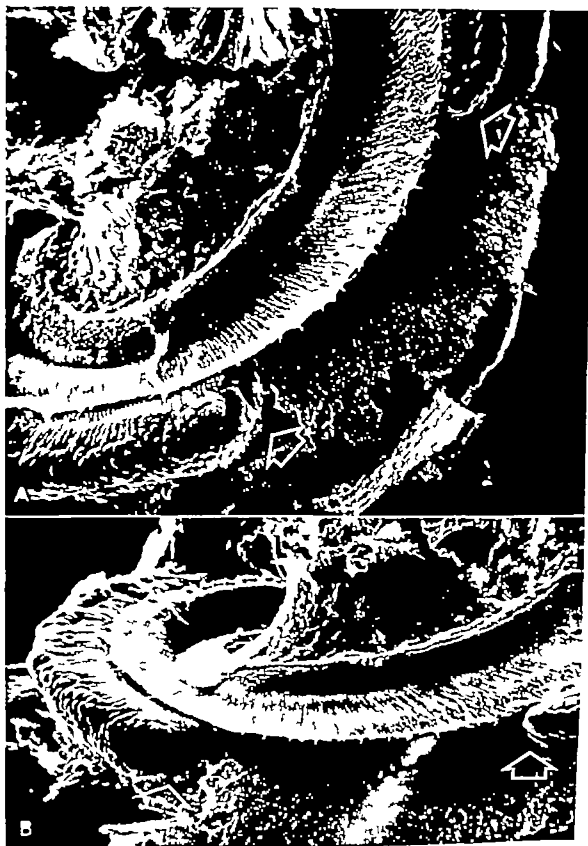


Fig 29 In A and B the same portion of a guinea pig cochlea has been studied in the scanning electron microscope The arrows indicate region of the cochlea completely degenerated through exposure to very high intensity noise (1.5 Hz, 148 dB for 4 hours) Over the organ of Corti the fibrillar tectorial membrane is seen Although the organ of Corti has disappeared completely in the injured area the tectorial membrane is still present. 195

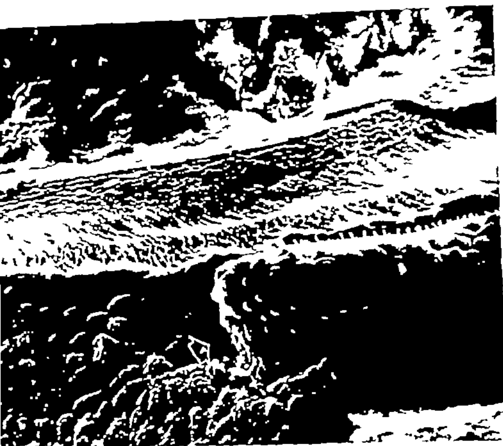


Fig 30 Detail from Fig 29 showing the sharp demarcation of the injured area. Observe that hair cells to the right of the damaged area are provided with hairs × 400

of the inner hair cells are tapered asymmetrically with the exception of the longest row on each cell (Fig 15)

Several thorough ultrastructural investigations have come about because of interest in the functional role of the sensory hairs as it relates to stimulation of the organ of Corti. These include studies by Engstrom et al. (1962) Kimura et al (1964) Wersall et al. (1965) Kimura (1966) Spoendlin (1966) and Wersall & Flock (1967)

The kinocilium of the cochlear hair cell forms a subject of particular interest and has been reported variously by different authors to be present, not present, or modified The vestibular sensory cells are supplied not only with stereocilia, but also with one kinocilium each Observations by light microscopy (van der Stricht, 1908 Held, 1909· Kolmer 1927) indicated a similar situation of the hairs on sensory cells in the mammalian organ of Corti however recent studies by transmission electron microscopy have claimed that, while a kinocilium is present during fetal and very early postnatal life (Kikuchi & Hilding, 1965 *a, b*· Kimura, 1966 Wersall & Flock, 1967), the sensory cells in the mature organ of Corti are devoid of this appendage. We have found that about one third

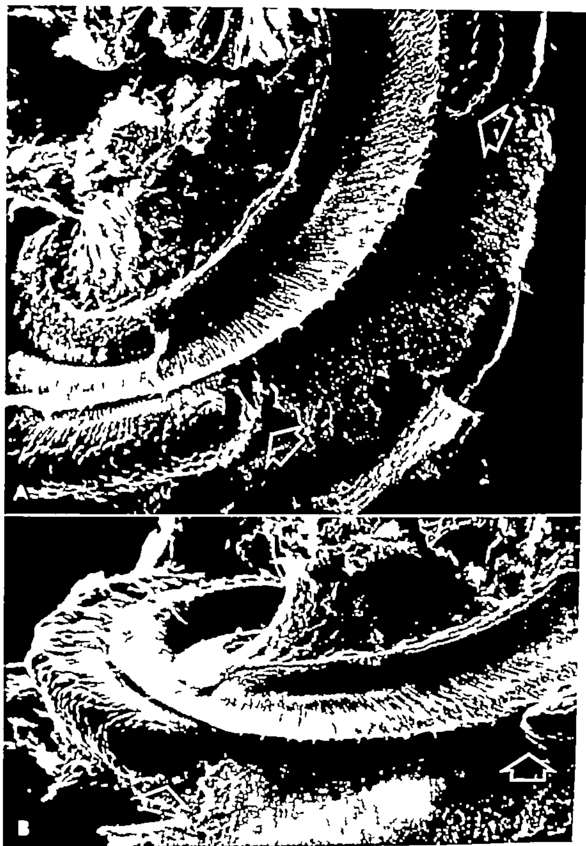


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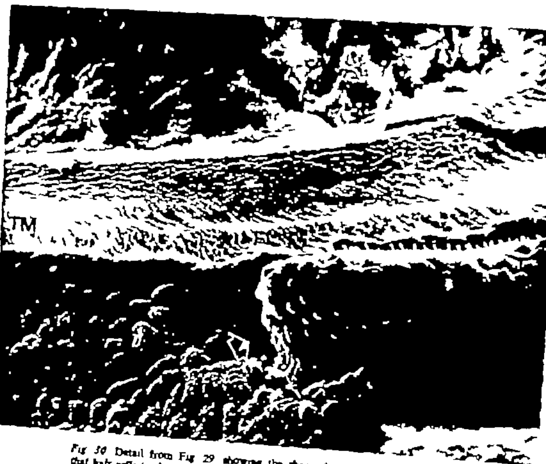


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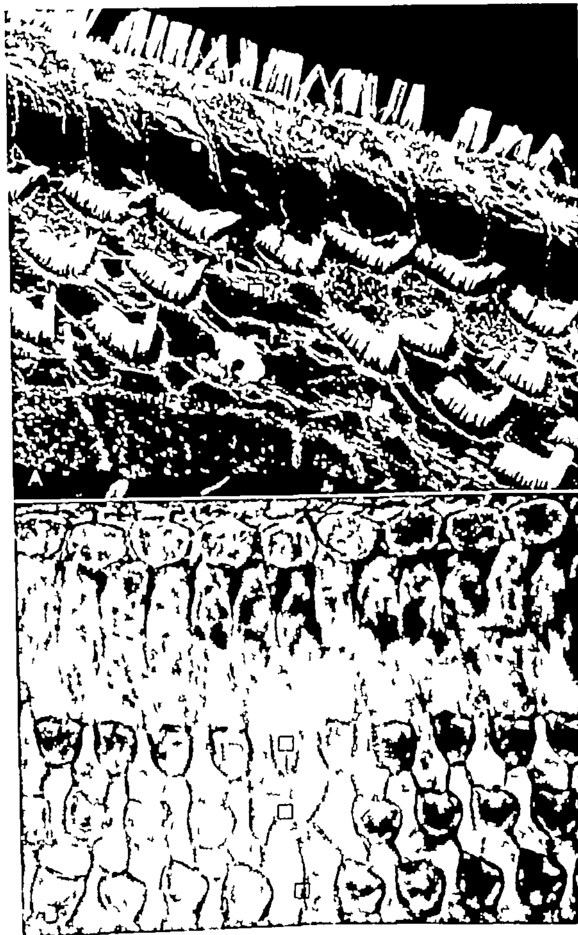

A



Fig. 32. The first and second row of outer hair cells, apical coil, of a sick cat in which it was impossible to obtain an audiogram by conditioning methods. The hair cells display severe pathology of the hair bundles including stereocilia with blebs or vacuoles, fusion of hairs and formation of giant hairs. Note the rich supply of microvilli on the supporting cells. × [illegible]

Fig. 31. I. A: the organ of Corti of a guinea pig has been exposed to gunshot noise and some cells are missing (squares). SEM. I. B: a similar damage can be seen in a squirrel monkey exposed to high intensity noise. In B we have used a surface specimen technique and phase contrast microscopy. (A) × 3 500, (B) × 1 530.

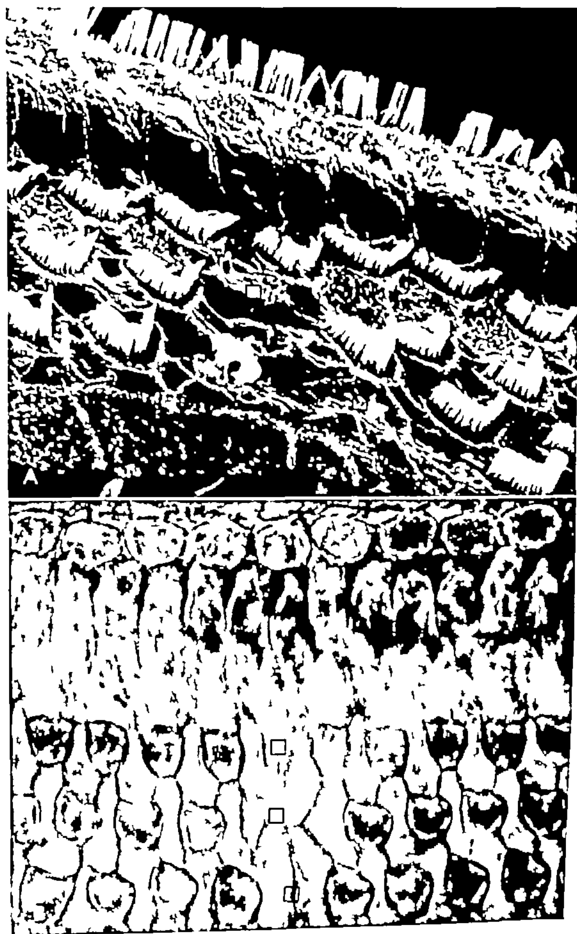




Fig 32 The first and second row of outer hair cells, apical coil, of a sick cat in which it was impossible to obtain an audiogram by conditioning methods The hair cells display severe pathology of the hair bundles including stereocilia with blebs or vacuoles, fusion of hairs and formation of giant hairs Note the rich supply of microvilli on the supporting cells × 8 200

Fig 31 In A the organ of Corti of a guinea pig has been exposed to gunshot noise and some cells are missing (squares) SEM In B a similar damage can be seen in a squirrel monkey exposed to high intensity noise In B we have used a surface specimen technique and phase contrast microscopy (A) × 3 500 (B) × 1 530



Fig. 33. Hairs on inner hair cells from the same cat as in Fig. 3. The general arrangement of the hairs is rather normal but the individual hairs have many irregularities especially at their outer ends. This can be found in normal specimens but is much more frequent in noise exposed animals. 10 600

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of the outer hair cells in the middle coil of cynomolgus monkeys (Macaca fascicularis) of approximately four years of age have rudimentary kinocilium like processes (Figs. 13, 18 B). Some few rudimentary kinocilium-like hairs can also be found on the outer hair cells of adult squirrel monkeys, which are neither as frequent nor as tall as those found in the cynomolgus monkey.

A basal body, believed to be a remnant of the kinocilium present during fetal life, is found in the corresponding cuticle free region just under the surface of the sensory cell from which it may even protrude slightly. The basal body has been found consistently in the guinea pig (Engström et al. 1962, Flock & Wersäll 1962) and the protrusion can be demonstrated in scanning electron microscopy (Fig. 12 D). On the other hand, Spoendlin (1966) has stated that the basal body is not to be found regularly in the cat. It is difficult to be sure



Fig. 34. These four micrographs show different stages in sensory hair deformation. In A there are seen several giant hairs on an outer hair cell from a human cochlea. In B, also from an old human ear, giant hair is seen protruding above the hairs of ordinary length. C and D. Guinea pig (upper basal coil), exposed to intense sound (4 000 Hz, 130 dB, 1 hour). There are slight irregularities on the individual hairs and in the arrangement of the rows of hairs. (A) ×5 200, (B) ×3 700, (C) ×8 700, (D) ×8 600.



Fig 33 Hairs on inner hair cells from the same cat as in Fig. 32. The general arrangement of the hairs is rather normal but the individual hairs have many irregularities especially at their outer ends. This can be found in normal specimens but is much more frequent in noise exposed animals 10 600

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is also characteristic that the concentration of microvilli is denser close to cell junctions (Figs. 4 6, 15 and 16). The supporting cells of the reticular membrane have relatively few the phalangeal processes of Deiters cells showing them to be fairly evenly distributed. The phalangeal processes of the outer pillar cells have even fewer almost exclusively close to the periphery of the cells. The inner pillar cell normally has very few microvilli. This is true also of the inner hair cells, although some of the stereocilia may be quite small, tending to merge with the microvilli in terms of size (Fig. 15). The dense distribution of the microvilli on the border cell (the cell closest to the inner hair cell on its modiolar side) is very striking (Figs. 4 6 15 and 16) The same dense distribution is obvious throughout all coils and all species studied so far (guinea pig, cat, monkey chinchilla, man). This can also be seen in the TEM (Fig 16). The microvilli are less densely distributed on the inner sulcus cells and again they are more numerous close to the cell borders.

In the human fetus, the microvilli of the organ of Corti are large and numerous, especially at the margins of hair cells. The supporting cells are also supplied with many microvilli, which appear to be more densely distributed in the fetal than in the adult man or animal (Figs. 17 18 A and 19) In certain animals (e g. mouse, cat, opossum) the cochlea is immature at birth. Specifically the cochlea of the newborn cat has microvilli which are larger and appear much more numerous than in the adult cat (Lindeman et al. 1971)

The afferent nerve fibers are supplied by bipolar ganglion cells whose soma lie in the spiral ganglion in the modiolus. The ganglion cells are distributed throughout Rosenthal s canal. It is possible to study these either by fracturing the frozen specimen (Fig. 20) or by direct dissection of the fixed specimen. These methods are as yet plagued by artefacts. In the dissected specimen, there is the additional factor of differential mechanical movement of the various elements in the structures which distorts the picture still more. Despite these difficulties, in Fig. 20 A the nucleus of the ganglion cell is clearly visible, and in the lower cell, even the nucleolus can be distinguished however the mye linated nerve fibers appear to be composed of empty shells of myelin, the axis cylinders which should occupy them being absent, which is, of course, an obvious artefact This is a problem which awaits resolution.

The peripheral dendrite of the afferent nerve runs through the osseous spiral lamina (Fig 20 B) out to the organ of Corti where it ends as a series of small and sparsely granulated nerve endings on the hair cells (Fig. 22) The dendrite loses its myelin sheath before penetrating the medial attachment of the basilar membrane. The dendrites making contact with the inner hair cells are believed to take mainly a radial course, whereas the dendrites associated with the outer hair cells take a spiral course of varying, unknown distance in the spiral bundles within the organ of Corti (Figs. 21 A and B) Fibers from several nerve endings and from several outer hair cells are branches of a single dendrite. The pattern of innervation in the organ of Corti is extremely complex and is yet far from clarification. Spoendlin (1966) estimated, in the cat, that the majority of the

by scanning electron microscopy whether or not it is present because there are usually a few microvilli scattered in the region

The organ of Corti of a three month old human fetus is shown in Figs. 17 18 A and 19 A kinocilium like structure can easily be recognized on each sensory and supporting cell Moreover it is interesting to note that the W *arrangement of the hairs is not yet developed* The *stereocilia* are *thickly* and uniformly distributed over the surface of the cells, there are no rows, nor any indication of the staircase like differentiation of the cilia into regularly recurring diminishing lengths.

The conformation of individual stereocilia has often been observed in scanning electron microscopy however surface structures such as stereocilia and microvilli are quite susceptible to artefact and difficult to assess as to normality or abnormality We have frequently observed small blister like "blebs" on the surface of stereocilia as discussed in an earlier paper by the present authors (Engström et al 1970) The blebs, which have been seen with both transmission electron microscopy (Fig 14) and scanning microscopy (Fig 12) occur in animals regarded as normal (because they had not previously been exposed deliberately to noise) They occur more frequently in the squirrel monkey and cynomolgus monkey than we have seen in other mammals. In ears that have been exposed to damage noise or ototoxic antibiotics changes in the stereocilia are common and they may be quite pronounced (Figs. 32, 33 and 34) Lim (1971) described blebs like those mentioned above in normal guinea pigs, but they were more numerous in acoustically stressed ears. Similar formations were also seen by Ernstson (1971) in transmission electron microscopy of the hair cells of waltzing guinea pigs. He alluded to them as vesiculated malformations because of their high content of vesicles.

Another observation which may be akin to the blebs is that of small inter connections or bridges between individual stereocilia (Figs. 6 and 15) These were seen primarily on the inner hair cells of cats. The nature of the bridges *is by no means clear and they may be artefacts* however the artefact may correspond to real structure, although possibly altered by the fixation or the freeze drying which is part of the preparation. Much thinner strands around both cochlear (Kimura, 1966) and vestibular (Engstrom et al. 1972 in press) sensory hairs have been seen by transmission electron microscopy For example they may be condensations of macromolecular aglomerations on the outer unit membrane of the stereocilia They are more frequently seen in association with inner rather than outer hair cells which may be an indication that it is due to a compound or compounds more abundant around inner hair cells. It may be also that they are more easily seen when associated with inner hair cells.

A phenomenon which scanning reveals very clearly *is the distribution of* microvilli The sensory cells themselves normally display very few of these but the supporting cells especially the Hensen cells (Fig 8) and the border cells have a rich supply of microvilli on the surface facing the scala media It

The appearance of the tympanic layer of the basilar membrane is particularly striking in scanning electron microscopy The arrangement of the cells is visible in light microscopy but the alignment in parallel, longitudinal rows is portrayed with clarity in scanning electron microscopy (Fig. 28)

THE APPEARANCE OF THE PATHOLOGICALLY ALTERED ORGAN OF CORTI IN THE SCANNING ELECTRON MICROSCOPE

The damaged organ of Corti has been examined by light/phase contrast microscopy and by transmission electron microscopy The picture in light/phase contrast has been described in a number of experimental studies and need not be reviewed here. Less complete studies by TEM have yielded a certain amount of information. In particular it has further revealed some additional features of damage at the ultrastructural level, such as the Hensen bodies and nuclear changes (which have also been seen to a more limited extent in light/phase contrast studies). Scanning electron microscopy has now been applied to the study of the impaired cochlea, and has presented a picture which adds considerably to those yielded by the other two methods.

The first observations were made at low magnification and show the overall lesion in a way not seen before. A guinea pig was exposed to a high intensity pure tone of 125 Hz (148 dB 4 hours) and sacrificed two weeks later The results are shown in Fig. 29 which shows two views of the same lesion, at the magnification indicated The lesion is in the apical coil It will be seen that there is a sharply limited area where the acoustic papilla is reduced to a simple cuboidal epithelium This can be observed better in Fig. 30 which is a scanning micrograph of one edge of the lesion at higher magnification. Interestingly enough, the tectorial membrane is still in its position above the degenerated area, and, so far as can be told, normal in its conformation. The transitional zone seems very short between an area of complete degeneration of the organ of Corti and one of apparently intact sensory organ

In an animal with less damage, sensory cells may be degenerated, but the general shape of the organ of Corti is still intact. A comparison between what may be seen in a scanning picture and a surface specimen is shown in Figure 31 Degeneration of receptor cells can be seen in both, but in the scanning picture the stereocilia can be seen as well, which becomes important in the circumstances described in the ensuing paragraph.

In experiments in which cats' audiograms were taken before and after exposure to intense sound, it was found on occasion that there was an apparent mismatch of audiometric loss and sensory cell population remaining: that is, there was a more profound hearing loss than seemed to be warranted by the cell loss. In a few cases, similarly exposed, SEM has revealed changes in the stereocilia of the hair cells The changes consisted of fusion of stereocilia with reduction of size, or a complete disappearance of hairs (seen in the more basal

afferent nerve endings terminate on the inner hair cells, only about one tenth extending to the outer hair cells The innervation of inner and outer hair cells as well as the functions of the inner and outer hair cells are presently debatable, and it is therefore inadvisable to make any firmer statements about these relations.

The *efferent innervation* of the cochlea has its origin from the contralateral accessory olivary nucleus, from the homolateral main superior olivary nucleus and from the reticular formation The efferent bundle enters the cochlea via the olivo-cochlear anastomosis (Oort's anastomosis) runs in Rosenthal's canal forming intraganglionic spiral bundles, and passes through the osseous spiral lamina taking a spiral course It terminates as large nerve endings on both inner and outer hair cells (Figs. 21 B 22, 23 and 24) Efferent nerve fibers are found in a spirally running bundle inside the tunnel of Corti the spiral tunnel bundle (STB) (Figs. 25 and 26) The size of the nerve fibers in this bundle varies considerably as seen in transmission electron microscopy In scanning electron microscopy the appearance of swellings ("beads") is very striking and it is possible that this explains some of the variation of caliber seen in transmission electron microscopy Thus the fiber size may in fact be more uniform than has been believed in the past (Figs. 26 A and B) and it may be only when a section is cut to include some fibers of normal size and some of the swollen fibers that one gets the mistaken impression that there is a considerable range of fiber size A number of the nerve fibers crossing the tunnel radiating tunnel fibers (RTF) pass through it, probably without branching or contact with the bundle (Fig 26 B)

The nerve fibers and the nerve endings which traverse or occupy a fluid filled space in the organ of Corti can be studied with minimal manipulation of the tissue but by dissecting the organ further observations can be made (Figs 6 20 21 and 23–26) The three-dimensional arrangement of nerve structures is very difficult to follow in light or conventional electron microscopy and here the scanning electron microscopy can be very helpful and adds much information The three methods may be compared in Figs. 21 22, and 23 The efferent nerve endings are larger than and partially enclose the smaller afferent endings (Figs. 21 and 22). The size of nerve endings diminishes as the apex of the cochlea is approached more closely The same phenomenon can be seen from medial to lateral, that is from OHC1 to OHC3

Reissner's (vestibular) membrane separates the scala media from the scala vestibuli being suspended between the spiral limbus and the vestibular crest of the spiral ligament. It consists of two layers of cells, one of ectodermal origin bordering the scala media and the other of mesodermal origin forming one border of the scala vestibuli (Fig. 27) The ectodermal portion is thicker than the mesodermal The two are separated by a thin basement membrane A few microvilli are seen on the cells of the ectodermal side In the scanning picture the bulging of the nuclei of the mesenchymal cells is prominent (Fig 27 B)

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THE APPEARANCE OF THE PATHOLOGICALLY ALTERED ORGAN OF CORTI IN THE SCANNING ELECTRON MICROSCOPE

The damaged organ of Corti has been examined by light/phase contrast microscopy and by transmission electron microscopy. The picture in light/phase contrast has been described in a number of experimental studies and need not be reviewed here. Less complete studies by TEM have yielded a certain amount of information. In particular it has further revealed some additional features of damage at the ultrastructural level, such as the Hensen bodies and nuclear changes (which have also been seen to a more limited extent in light/phase contrast studies). Scanning electron microscopy has now been applied to the study of the impaired cochlea, and has presented a picture which adds considerably to those yielded by the other two methods.

The first observations were made at low magnification and show the overall lesion in a way not seen before. A guinea pig was exposed to a high intensity pure tone of 125 Hz (148 dB 4 hours) and sacrificed two weeks later. The results are shown in Fig. 29 which shows two views of the same lesion, at the magnification indicated. The lesion is in the apical coil. It will be seen that there is a sharply limited area where the acoustic papilla is reduced to a simple cuboidal epithelium. This can be observed better in Fig. 30 which is a scanning micrograph of one edge of the lesion at higher magnification. Interestingly enough, the tectorial membrane is still in its position above the degenerated area, and, so far as can be told, normal in its conformation. The transitional zone seems very short between an area of complete degeneration of the organ of Corti and one of apparently intact sensory organ.

In an animal with less damage, sensory cells may be degenerated, but the general shape of the organ of Corti is still intact. A comparison between what may be seen in a scanning picture and a surface specimen is shown in Figure 31. Degeneration of receptor cells can be seen in both, *but in* the scanning picture, the stereocilia can be seen as well, which becomes important in the circumstances described in the ensuing paragraph.

In experiments in which cats audiograms were taken before and after exposure to intense sound, it was found on occasion that there was an apparent mismatch of audiometric loss and sensory cell population remaining: that is, there was a more profound hearing loss than seemed to be warranted by the cell loss. In a few cases, similarly exposed, SEM has revealed changes in the stereocilia of the hair cells. The changes consisted of fusion of stereocilia with reduction of size, or a complete disappearance of hairs (seen in the more basal

afferent nerve endings terminate on the inner hair cells, only about one tenth extending to the outer hair cells. The *innervation of inner and outer hair cells* as well as the functions of the inner and outer hair cells are presently debatable, and it is therefore inadvisable to make any firmer statements about these relations.

The *efferent innervation* of the cochlea has its origin from the contralateral accessory olivary nucleus, from the homolateral main superior olivary nucleus and from the reticular formation The efferent bundle enters the cochlea via the olivo-cochlear anastomosis (Oort s anastomosis) runs in Rosenthal s canal forming intraganglionic spiral bundles, and passes through the osseous spiral lamina taking a spiral course. It terminates as large nerve endings on both inner and outer hair cells (Figs. 21 B 22, 23 and 24) Efferent nerve fibers are found in a spirally running bundle inside the tunnel of Corti the spiral tunnel bundle (STB) (Figs. 25 and 26) The size of the nerve fibers in this bundle varies *considerably as seen in transmission electron microscopy In* scanning electron microscopy the appearance of swellings (beads") is very striking and it is possible that this explains some of the variation of caliber seen in transmission electron microscopy Thus the fiber size may in fact be more uniform than has been believed in the past (Figs. 26 A and B) and it may be only when a section is cut to include some fibers of normal size and some of the swollen fibers that one gets the mistaken impression that there is a considerable range of fiber size A number of the nerve fibers crossing the tunnel radiating tunnel fibers (RTF) pass through it probably without branching or contact with the bundle (Fig 26 B)

The nerve fibers and the nerve endings which traverse or occupy a fluid filled space in the organ of Corti can be studied with minimal manipulation of the tissue but by dissecting the organ further observations can be made *(Figs. 6 20 21 and 23–26) The three-dimensional arrangement of nerve structures* is very difficult to follow in light or conventional electron microscopy and here the scanning electron microscopy can be very helpful and adds much information The three methods may be compared in Figs. 21 22, and 23 The efferent nerve endings are larger than and partially enclose the smaller afferent endings (Figs. 21 and 22) The size of nerve endings diminishes as the apex of the cochlea is approached more closely The same phenomenon can be seen from medial to lateral that is from OHC1 to OHC3

Reissner s (vestibular) membrane separates the scala media from the scala vestibuli being suspended between the spiral limbus and the vestibular crest *of the spiral ligament It consists of two layers of* cells one of ectodermal origin bordering the scala media, and the other of mesodermal origin forming one border of the scala vestibuli (Fig 27) The ectodermal portion is thicker than the mesodermal The two are separated by a thin basement membrane A few microvilli are seen on the cells of the ectodermal side. In the scanning picture the bulging of the nuclei of the mesenchymal cells is prominent (Fig 27 B)

at × 100 to 10 μ at × 10 000 This quality of the scanning electron microscope makes it a superb instrument for the study of surface topography

The study of the interior structure of cells by scanning electron microscopy so far remains a problem The process of preparing a specimen, dissection, fixing or freeze-drying, induces artefacts. The cytoplasm of a cell condenses and retracts: the result is a non-homogeneous structure filled with apparent vacuoles (Figs 9 and 20) Great caution must be exercised in the interpretation of these pictures so that artefact is not taken to represent true morphological structure. For example in Fig. 20, if the hollow cylinders which represent the nerve fibers were to be interpreted literally one would conclude that the nerve fiber is a hollow tube, because only the myelin sheath remains more or less intact with fibrous looking material occasionally bridging across the gap that should represent the axoplasm. The axoplasm itself is gone. Likewise but less obviously the lacunae which are seen throughout the cytoplasmic and nuclear areas of the somata, might be interpreted as real structure which would be equally mistaken in the interpretation of Figs. 1 9 20, and 25 The wrinkles in the sensory cell seen in Fig 23 are artefacts in all probability and therefore potentially misleading Evidence of pronounced artefacts are also present in other early publications. Further experience in the techniques of preparation may reduce the artefacts to more manageable proportions however some of the artefacts have no apparent solutions as yet, and will yield only to new concepts of preparation.

The statement was made in the Introduction that scanning electron microscopy does not supplant either transmission electron microscopy or light/phase contrast microscopy The combination of scanning electron microscopy with one or the other seems to hold some promise of advancing our understanding of the ear and reducing the effects of artefact, or at least of changing the artefacts into a form with which we are more accustomed to dealing. Barber & Boyde (1968) for example, tried the combination of studying a specimen by scanning electron microscopy first and then embedding it for sectioning and study by transmission electron microscopy demonstrating surprisingly good preservation of the specimen in the transmission electron microscopy

The combination of light/phase contrast with scanning electron microscopy has also been shown to work quite well as applied to the cilia (Lindeman & Bredberg, 1972). Specimens first examined by light/phase contrast to obtain the advantage of mapping, were subsequently taken from under the cover glass and prepared for scanning electron microscopy and the two were compared. It was found that to all intents and purposes they were equally as good as those prepared first for light/phase contrast, showing only some flattening of cilia from the pressure of the cover glass.

The combination of light/phase contrast with transmission electron microscopy has also been shown to be quite feasible again going from the one to the other in that order cutting out small segments from known positions to embed This has the effect of overcoming to some extent the loss of overall

portion of the cochlea (Fig 34 C D) In the more apical portion a fusion and growth of the stereocilia to "giant" hair size may occur Similar changes have been observed in a sick cat (Fig 32) Figs. 34 A and B demonstrate changes in the stereocilia of elderly human subjects. It may be seen that there is gross dis organization of the hairs and formation of giant hairs. This is a subject without known exposure to noise but of course he may well have been exposed

Simple fusion of stereocilia has been described by Kimura (1966) and Kimura et al (1964) reported giant hairs in the human organ of Corti. Crysdale & Stahle (1971) observed severe pathology of the stereocilia following ultrasonic irradia tion of the cochlea in guinea pigs, and Stahle et al (1971) also described changes of the stereocilia after laser beam irradiation Ernstson (1971) observed similar structural modifications in the waltzing guinea pig associated with extrusion of cytoplasm from the cell into the stereocilia Fusion of stereocilia has been reported in the vestibular epithelium as a result of administration of ototoxic antibiotics (Duvall & Wersäll, 1963 Nagaba 1968 Lindeman 1969 Wersäll et al 1971) following X ray irradiation (Winther 1970) and in the waltzing guinea pig (Ernstson et al. 1969)

In view of these findings, described more extensively by Lindeman & Bred berg (1972) *it appears that fusion overgrowth and other changes in the* stereocilia constitute a non-specific reaction to a variety of noxious influences. This may indicate that damage to some basic structure or biochemical reaction has occurred which causes these changes. Which basic structure or what bio-chemical reaction this may be is an open question That the changes in the stereocilia may result in functional impairment is probable. The mechanical event which stimulates the sensory cell is generally conceded to be the shearing movement between the tectorial membrane and the sensory hairs, the longest of which are in contact with the membrane The pathological changes may interfere with this relationship in various ways. It could be at the level of contact which is certainly altered. Likewise it could be in an altered lever action of the stereocilia

The supporting cells, as well as the sensory cells responded to auditory over stimulation by an increase in the number and size of microvilli This was a phenomenon which was clearest in those ears showing the most pronounced changes in the sensory cells. Abundance of microvilli is generally associated with cells whose principal function is absorption Whether this increase fol *lowing acoustic overstimulation is a sign of increase in* absorptive functions of the supporting cells, or points to some other function is not clear

DISCUSSION

The obvious and striking advantage of the scanning electron microscope is the formation of a three-dimensional picture with good resolution and a good depth of field The field depth varies inversely with magnification from 1 mm

at ×100 to 10 μ at ×10 000 This quality of the scanning electron microscope makes it a superb instrument for the study of surface topography

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orientation characteristic of transmission electron microscopy but so far it allows only for a sampling albeit a rational sampling The reverse order of study between scanning electron microscopy and transmission electron microscopy is not so feasible, inasmuch as the scanning electron microscopy artefacts are built into their subsequent study by transmission electron microscopy This is a problem that remains to be solved The procedure to be most useful, should produce in either order for either method in combination with scanning electron microscopy

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Supporting Elements in the Organ of Corti

I. *Fibrillar structures in the supporting cells of the organ of Corti of mammals*

by Clarence Angelborg and Hans Engström[1]

During the last decade the interest in the structures of the inner ear has increased considerably This interest depends upon several factors. The increasing knowledge of inner ear physiology has probably been the dominating factor but the development of new techniques for structural analysis has also played a major role. Transmission electron microscopy (TEM) has been the outstanding technique for structural analysis and has considerably enriched our knowledge of the organ of Corti. Recently an interesting new technique has become available in the form of scanning electron microscopy (SEM)

In the majority of the numerous articles written on the ultrastructure of the organ of Corti in recent years, the main interest has been devoted to the sensory cells and rather little has been said about the supporting elements in the cochlear duct In relation to their studies on the inner ear fluids, Ilberg (1968) Ilberg & Vosteen (1969) among others made very few comments on the functional properties of the supporting cells. Duvall & Quick (1969) observed tracers in the Claudius cells after intrathecal injection of thorotrast.

During a series of experiments dealing with the passage of fluids between the different compartments in the cochlea, Angelborg (unpublished data) found evidence of high functional activity in several of the supporting cells. Cells regarded earlier as having a supporting function, gave evidence of pronounced phagocytic activity much more so than we had previously imagined. It also became evident that cellular damage could radically change the mode of action of the cells Therefore further studies on the normal structure of the supporting cells have been started and these studies have been combined with experiments on the functional behaviour of the cells In our first attacks on the problem we found a previously unknown principle in the arrangement of the tonofibrils in the pillar cells and Deiters cells. This contributed to our increased interest in the supporting structures of the organ of Corti.

Angelborg and collaborators are now carrying out studies on the structure and function of the supporting elements in the organ of Corti. The first paper contains a description of the normal anatomy of the pillar cells and Deiters' cells.

[1] Dept of Otolaryngology University of Uppsala, Sweden

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Fig. 2. Cross section through the middle portion of an outer pillar cell. This picture illustrates in a very beautiful way the tubular nature of the filaments. It is also possible to see some of the interspaced microfilaments. Guinea pig. TEM × 58 000.

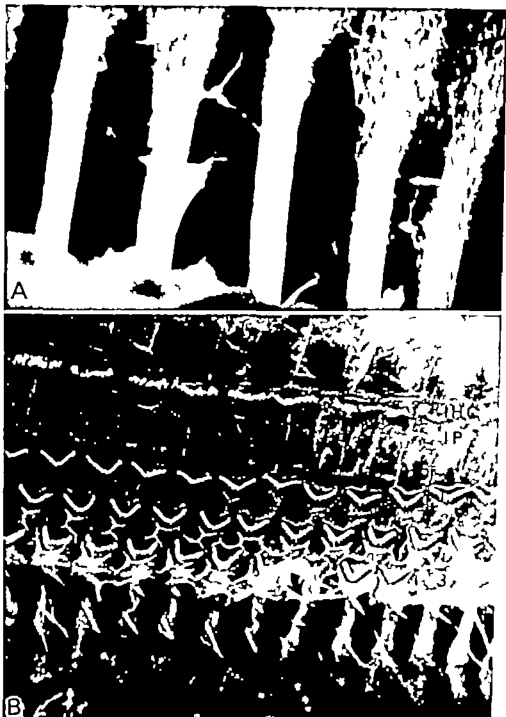


Fig. 1. (A) Outer pillars with nerve fibers passing between the cells. Squirrel monkey. SEM. (B) The organ of Corti as seen from the surface showing the heads of the inner pillar cells. Above these can be seen the heads of the inner hair cells and below three rows of outer hair cells. This portion is from the lower half of the cochlea and the angle between the hair rows is about 90 degrees. The picture also shows the outer edge of the third row of hair cells and the outermost row of phalangeal processes of the Deiters cells. Guinea pig. SEM.

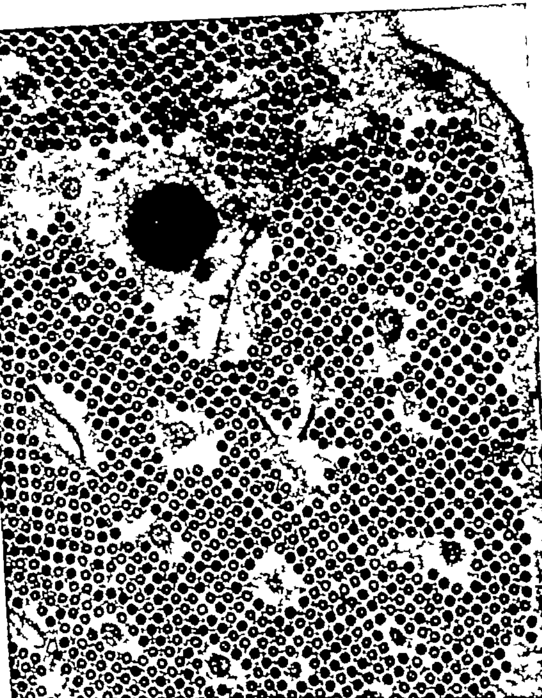


Fig. 3. Higher magnification of cross-sectioned outer pillar cell. At this magnification the tube-like filaments and the interspaced microfilaments are easily seen. Gulton pig. TEM × 114 200

FIBRILLAR STRUCTURES IN THE SUPPORTING CELLS

The outstanding publication on the structure of the supporting elements in the *organ of Corti* was published in 1926 by Held and described the supporting cells and their inner structure. These cells are the inner and outer tunnel rods or pillar cells, the inner and outer phalangeal cells and the border cells axially *of the inner hair cells. The first description of the* pillar cells was given by Corti (1851) and Kölliker (1852) observed fibrillar structures inside the pillar cells. In a series of publications these cells were then described by different authors and Retzius (1884) presented beautiful illustrations of the supporting cells and their relations to the sensory cells and to the basilar membrane.

In each pillar cell (Pfeilerzell) Held describes a "footplate" adhering to the basilar membrane, a "middle-portion" and "head portion" In the inner pillar this last part forms a head plate" and an "Innenschabel" which enters between two inner hair cells, forming a triangular extension from the head portion. The outer pillar cells reach the surface outside the inner pillar head plate with an "oarshaped" plate (Ausenruder) which contributes to the formation of the surface of the organ of Corti and forms contact with the first and second row of outer hair cells

The middle portion of the inner pillar is rather flat and in the narrow spaces between individual cells, nerve fibres pass from the inner spiral bundle region to the tunnel and to outer hair cells. The middle portion of the outer pillar is more cylindrical (Fig 1 A) and contains large numbers of fibrils which are densely packed so that they form a fiber rod (Faserstab Held, 1926)

In many mammals and especially in rodents, the head portion contains a head inclusion or head body (Kopfeinschluss, Joseph 1900 Kopfkörper Held, 1926) This inclusion is rather electron dense The basal portion of both inner and outer pillars contains a similar substance forming the "basal cone" (Basal körperchen Held) (Fig 7) Held and others regarded this cone, which may have a varying height as a reinforcement for the anchorage of the tonofibrils. During the years there have been many descriptions of the supporting cells. Electron microscopy was introduced to these studies by Engstrom & Wersäll (1953) who gave a description of the cells and found tonofibrils with a diameter of around 200 A. These fibrils could be followed for a long distance inside the pillars and it was postulated that they reached from the base of the pillar to the top where they took part in the formation of the reticular membrane

Further information regarding the tonofibrils came in 1967 in a study by Iurato He found that they consisted of protein and that in the rat they had a diameter of 215 A and formed a cuboid lattice having a periodicity of 420 A. He found in the densely packed regions 570 filaments per square micron in outer pillars, while the density was lower in inner pillars Iurato compares the tonofibrils with the filaments of different plants and animals cells, described "as cytoskeletal structures associated with the maintenance of highly asymmetrical cell shapes" Iurato also found a different number of tonofibrils depending upon

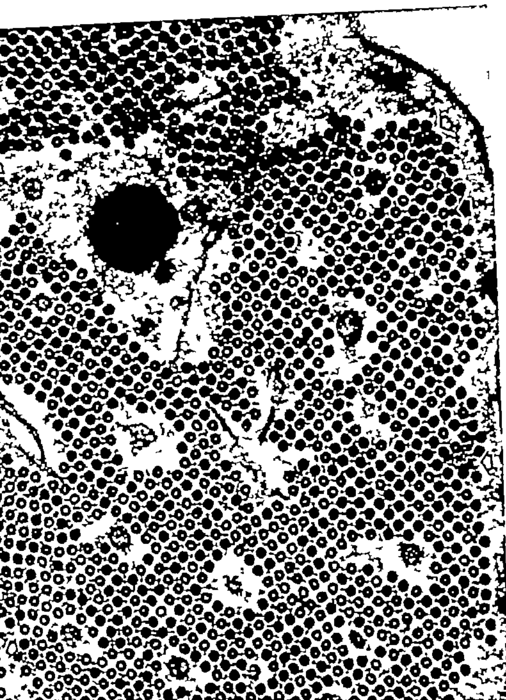


Fig. 3. Higher magnification of cross-sectioned outer pillar cell. At this magnification the tubule-like filaments and the interspaced microfilaments are easily seen. Guinea pig. TEM ×114 200

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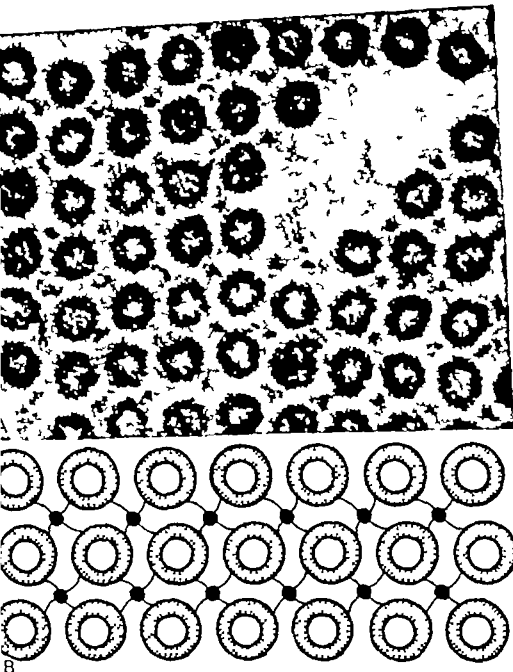


Fig 5 (A) Tube-like and solid filaments in an outer pillar cell Guinea pig EM × 440 000 (B) A schematic drawing of the arrangement of the tube-like filaments and the microfilaments The picture also shows some of the macromolecular bonds between the two different kinds of filaments It is also common to find two microfilaments in each interspace

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Fig 4 A and B, cross sections, C, longitudinal section of outer pillar cells In A and B it is possible to discern both the tube-like filaments and the microfilaments which are much more numerous in certain regions In the longitudinal section, C, the two different kinds of fibers can also be seen Arrows indicate microfilaments Guinea pig TEM (A) × 11 000 (B) × 150 000, (C) × 130 000

A



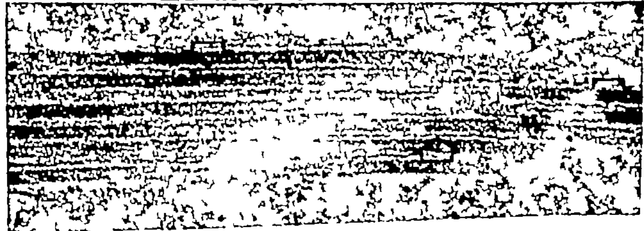




Fig. 7. Base of an inner pillar cell resting on the basilar membrane. The basilar core can readily be observed and some of the tonofilaments are enclosed by the cementlike structure. A majority of the fibers start around the cone-like formation and there is also a large number of mitochondria in this region. To the right of the base of the pillar can be seen the nerve fibers belonging to the inner spiral bundle. Squirrel monkey. TEM. × 11 000.

(C) Section at right angle to Fig. 6A. To the left an outer hair cell and to the right Deiters' cell. Inside the Deiters' cell a few tube-like filaments are on their way up to the cup-shaped part of the cell. They form a reinforcement that is attached to the sensory cell. Here we also can find a tendency to cementlike formation. Squirrel monkey. TEM. (A) × 134 000. (B) × 60 000. (C) × 45 000.



Fig. 6. (A) The junction between an outer hair cell and a Deiters cell. The microfilaments are seen between the plasma membrane of the Deiters cell and the tube-like filaments and also between the individual tubular filaments. (B) Longitudinal section through an outer pillar cell showing the parallel arrangement and dense packing of the tubular filaments.

section of the reticular lamina which surrounds the first row of outer hair cells.

In the outer pillars the filaments also originate in the basal cone where they have their origin in a wide area. The fibrils then become densely packed in the middle portion (Figs. 2, 3, 5) where they are arranged with almost geometrical regularity. In the head portion they fan out again and insert into the head inclusion and penetrate towards the outer hair cells where they participate in the formation of the reticular lamina. It was stated earlier that the filaments had a tubular nature and in the 60 Å thick wall there is indication of some kind of denser sub-unit (Fig. 5) the nature of which we have not been able to discover. Each tubule runs for a long distance, presumably from the basilar membrane region to the reticular lamina. The arrangement of the tonofibrils at the base and in the head region indicates that they have an important function for mechanical reinforcement.

Beside and between the tubular tonofilaments there is a second system of microfilaments with a thickness of around 60 Å. These filaments are much more numerous in certain parts of the pillars. In the central densely packed part of the middle portion of the outer pillars they are seen interspaced between the tubular filaments as seen in Figs. 3, 4 and 5 and in the schematic figure. These long microfilaments are provided with some molecular bonds which connect them to the tubular filaments. As far as we can find they run in the same manner as the tubular filaments presumably from base to top. The microfilaments follow close to the tubular filaments where they diverge at the top and base. The solitary fibrils diverging at the basal cone seem to retain a rather constant distance from a nearby tubular filament.

In the inner pillars we also find both the tubular filaments and the microfilaments and in those regions where the tubuli are closely packed the arrangement resembles that of the outer pillars. In certain areas where the arrangement of the tubular tonofibrils is less dense and at the periphery of the bundles of tubules, considerably more microfilaments than tubuli can be found.

In the Deiters cells the same two kinds of filaments are found. They begin at the basal end of the Deiters' cells in the small cementlike cone found close to the basilar membrane. In the dense thin columnar bundle of tubular tonofibrils seen in the lower part the thin microfilaments are interspersed between the tubules in the same manner as in the pillar cells. Close to the hair cell bases where some of the tubular tonofibrils form a cupshaped reinforcement they form a single layer of microfilaments between the plasma membrane and the tubular filaments. A few, usually two, microfilaments are also seen between the individual tubules (Fig. 6). At the outer hair cell bases the microfilaments are thus much more numerous than the tubular filaments. In the guinea pig we have found the relation to be 5:1 in some regions we have counted. We have not studied tonofilaments in the inner phalangeal cells or in the border cells.

We have observed, as stated previously, two systems of tonofilaments with different structures and presumably different properties. The structural organiza-

the age of his animals (rat) In the young rat there were about 2 500 filaments per pillar in the basal coil, 2 000 in the middle coil and 1 000 in the apical coil. In the adult rat he found 3 000–4 000 per pillar in the basal and middle coils and 1 500–2 000 per pillar in the apical whorl

Smith & Takasaka have recently (1971) given a description of the supporting cells in different animals In mammals they found tonofilaments or microtubules approximately 230 Å in diameter with thickened walls. They found that the tubule extended from the basal end of each pillar to the surface of the organ of Corti They also observed that the single units are bound together by some material and regarded this to be of importance for the strength of the supporting structures.

The Deiters cells *contain similar tonofilaments and occasional fibrils have* been observed *in inner phalangeal cells and border cells (Held, 1926) The fila*ments reach the surface of the organ of Corti where they take part in the formation of the reticular lamina. The word *lamina reticularis* was established by Kölliker (1852) and it is now widely used to describe the reticular lamina formed at the surface of the organ of Corti. It consists of supporting cells and their tonofibrillar structures and also a dense fine granular reinforcement found outside the hair cells into which the tonofibrils insert This granular structure seems to be of the same structure in the basal cones of the pillar cells and in the region where the tonofibrils of Deiters cells extend from the basilar membrane The resemblance to the head inclusions and to the reinforcements around the hair cells is also very evident. It is probable that they all form a kind of cementlike substance for the anchorage of tonofilaments at the basilar *membrane and at the surface of the organ of Corti In some animals a thin* layer of a similar substance can be found close to the bases of outer hair cells where some tonofibrils also insert forming a cup-shaped support for the hair cells.

In relation to an extensive study of the structure and function of the supporting cells carried out by Angelborg we had reason to study the tonofilaments of the supporting cells described above. We found that *both pillar cells and Deiters cells contain two different kinds of filaments* in the animals we have studied (guinea pig squirrel monkey cat, chinchilla and rat)

The most prominent filament is of a tubular nature In the middle coil of young guinea pigs they number about 2 400 and in the squirrel monkey they were counted in three adjacent pillar cells as *1 226 1 315 1 463* We *have studied* them very closely in the guinea pig and squirrel monkey In the middle coil of the guinea pig (Figs. 2 3 4 5) they have an outer diameter of approximately 275 Å They are tubular in form and they have a wall thickness of around 60 Å In the inner pillars they are slightly irregularly arranged They start at the basilar membrane region in the cementlike substance of the basal cone which often has a lighter center and a denser outer portion They then become more densely packed in the middle portion and in the head they *fan out to the* reticular membrane close to the inner hair cells and *the outer pillars. But many* filaments also run over the heads of the outer pillars to become part of that

Stria Vascularis

by Jerome O. Sugar[1] Hans Engström and Jan Stahle[2]

INTRODUCTION

The vascular supply of the inner ear has been the subject of many investigations during the past century. One area in particular the vascular stria has claimed the interest of numerous researchers during this period. This region of the membraneous labyrinth has been described in numerous papers with the use of many different injection and staining techniques.

The stria vascularis was first observed by Corti (1851) and also described by Eichler (1892), who used India ink to show its vessels. In 1894 Siebenmann used Prussian blue to demonstrate the stria. Shambaugh (1903) described the stria vascularis as well as other capillary areas in the ear. Nabeya (1923) used Prussian blue, Smith (1951) used the benzidine method and lead chromate and Axelsson (1968) who used Prussian blue are among some of the more recent investigators of the capillary area in the lateral cochlear wall. Axelsson's study stands out among the more recent papers for its thoroughness in documenting the basic vascular anatomy of the cochlea in the guinea pig and in man. This recent paper meant, among other things, to bring order to the maze of terminology used in reference to the vascular channels of the cochlea.

The use of transmission electron microscopy in describing the ultrastructure of the stria vascularis was pioneered by Engström et al. (1955). Since then Smith (1957), Hinojosa (1966) and Kimura (1970) are among the many authors who have added greatly to our fundamental knowledge of the fine structure of this tissue.

In all the investigations of the stria vascularis done by light microscopy the problem of reproducibility of results and easiness of methodology stands out as being a constant problem. Smith (1954) observed in her human material that there was "considerable variation in distension of the vessels" with use of the benzidine staining method. Axelsson attempted in his monograph to bring an element of constancy to his preparations by only using the Prussian blue injection technique. In his study there was a constant problem of filling the stria capillaries. Thus Axelsson pointed out that in the guinea pig, "a common exception was the stria vascularis where small parts of the capillary net often were uninjected". In his human material, "the stria vascularis and the capillary region in the spiral lamina proved particularly difficult to fill completely".

[1] Visiting research fellow. University of Illinois, College of Medicine and Graduate College, USA.

[2] Dept. of Otolaryngology. University of Uppsala, Sweden

tion of the pillars and the Deiters cells indicates that they are provided with a very well developed mechanical reinforcement system. The two systems of fibrils are anchored at their basal ends in a cementlike substance closely attached to the basilar membrane They are also bound together by as yet unidentified macromolecular interconnections. At the heads of the pillars the head inclusions form insertions for filaments. These form an important part of the reticular lamina in which they insert close to the outer and inner hair cells. In the basal portion of the cochlea the border between the outer pillar cells and the basilar membrane is often corrugated or irregular This presumably indicates a special differentiation for increased adherence (Fig 7)

SUMMARY

The pillar cells and the Deiters cells in the organ of Corti of mammals studied contain two kinds of tonofilaments bound together by macromolecular bonds In the squirrel monkey and guinea pig some filaments have a thickness of 275 Å and are tubular The tubular wall has a thickness of 60 Å We recommend that they should be called *tubular filaments.*

The other filamentous structures which we would name *microfilaments* have a diameter of 60 Å The microfilaments appear solid in our specimens and like the tubular filaments they are quite long. We believe they reach from the basilar membrane to the reticular lamina

A description is given of the fibrillar arrangement which indicates that the fibrils have a function of mechanical reinforcement.

Finally it is evident that if we are going to evaluate minor changes in the inner ear under the influence of damaging factors a good knowledge of the normal components is imperative.

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Mass (1969) was able to achieve extremely good results in filling the stria vascularis as well as the rest of the vessels in the cochlea, but the difficulty of his modified benzidine method prevents its routine usefulness.

The problem of achieving a constant, physiologic appearance of the blood vessels in the lateral cochlear wall prompted this present study Our two goals in the investigation were to demonstrate without fail the stria vascularis and the other blood vessels in the cochlea We also wanted to develop a method that would be simple to use and could be performed without destroying the usefulness of the surrounding tissues for transmission and scanning electron microscopy

This paper is a preliminary report about a method that can be started within minutes prior to sacrificing an animal. This is followed by a microdissection of the inner ear and when this is completed the blood vessels can be visualized within a few minutes The results are excellent, they are reproducible and the specimens can be made quickly with a minimum of technical details. In the preparations it is possible to survey the vascular anatomy of the inner ear in part or in toto

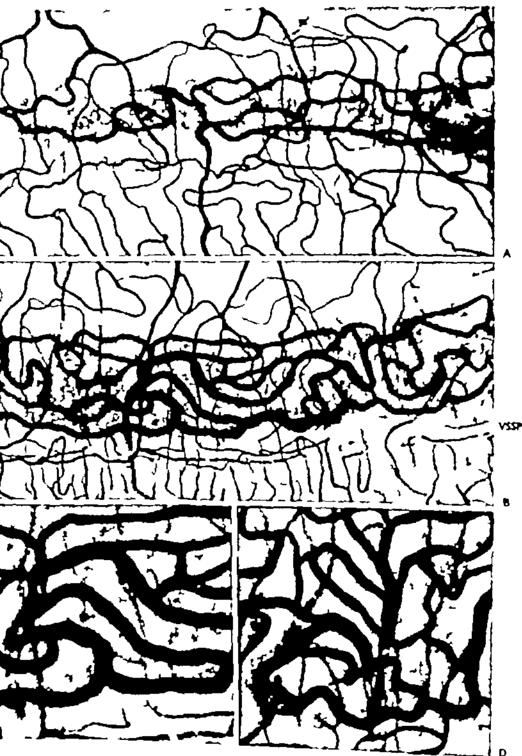
MATERIALS AND METHODS

Because of the various experimental variables that were investigated in deter mining the optimum conditions for demonstration of the vascular anatomy the method will be presented in an experimental section and a preferred method section

Experimental section

50 pigmented guinea pigs (150–300 g) of the same strain were used in the present study The animals were anesthetized by an intraperitoneal injection of Nembutal (Abbott Laboratories, Chicago Ill) 20 mg/kg The animals were shaved clean of hair on the ventral aspect of the mandible and neck. The area over the mandible was infiltrated with subcutaneous 0 5% Xylocaine® and an incision of approximately 6 cm was made in the region over the ventral aspect of the mandible. The external jugular vein was exposed and horseradish per oxidase (Type II Sigma Chemical Co Saint Louis Missouri) dissolved in saline, sterile water or 0 9% NaCl 5–20 mg/100 g was injected intraveneously using a 27 gauge Luer Lok needle The animals were allowed to survive between

Fig 1 (A) Stria vascularis from the top coil of a guinea pig cochlea. In this coil there is a very simple or little developed system of blood vessels in the stria. (B) Stria – coils from the top showing a richer system of blood vessels. The arterial and venous vessel can be seen as well as the richly interconnected blood vessels of the stria *(C and D) Stria* from the lower part of the cochlea of guinea pig showing the rich vascular network in the basal portion Figs 1 A, B, C and D all show the result of the present *technique They* demonstrate how the whole vessels and all vessels are *stained The staining is very* constant In this case we have chosen an incubation time which gives an orange-red colour It is possible to vary this colour to brown or blue.


A
VSSP
B
D

30 seconds and 1 1/2 hours after injection of the horseradish peroxidase. They were then decapitated and their bullæ removed.

The stapes was lifted out, the round window perforated and the apex of the cochlea opened prior to circulation of the fixation fluid. The following fixations were tried. 2% glutaraldehyde in 0.2 M phosphate buffer pH 7.4 2.5% glutaraldehyde, pH 4.4 2.5% glutaraldehyde in 0.07 M Sörensen's buffer pH 7.4 2.5% glutaraldehyde in 0.1 M phosphate buffer pH 7.4 10% formaldehyde pH 4.5 10% formaldehyde with 30% sucrose, pH 4.7 The fixatives were introduced through the oval window and gently circulated throughout the cochlea. In addition fixative was perfused through the round window and the apex. After fixation the specimens were either left in room temperature from 2–24 hours or refrigerated for 2–4 hours. Next the ears were rinsed in sterile water saline or buffer and then left either in veronal, phosphate or Sorensen's buffer The desired ears, either whole or in selected portions were incubated in a medium of 3–5 mg of 3,3'-diaminobenzidine tetrahydrochloride (Sigma Chemical Co Saint Louis, Missouri), or benzidine, 10 ml of buffer (phosphate, Sorensen or Tris buffer) and 0.1 ml of 1–3% H_2O_2 freshly prepared from 30% H_2O_2. The incubation medium was changed every 10 minutes and if the whole cochlea was incubated the fluid was circulated. The time of incubation was between 10 minutes and two hours. After incubation the desired portion or the whole cochlea was rinsed three times in distilled water during a 45 minute period. The cochlea was then either dissected, or the freed pieces were mounted in glycerine or Zeiss Embedding medium (ind. 1.50). If Canada balsam was used for mounting the tissues were dehydrated. After fixation some specimens were decalcified for one week in either 5% nitric acid or EDTA and after rinsing in buffer processed as previously stated

Photography was done with a Zeiss Ultropak or a Wild microscope.

Preferred method

Guinea pigs are intraveneously injected with horseradish peroxidase dissolved in 1 ml of sterile water 15 mg/100 g body weight and are allowed to survive for 10 minutes The animals are decapitated and the bulla fixed with 2.5% glutaraldehyde in 0.07 M Sorensen's buffer for 4 hours at 0–4 C. The ears are rinsed in saline and then stored at 0–4 C in 0.07 M Sörensen's buffer with sucrose Prior to incubation, the specimens are transferred to veronal buffer This buffer is used as the medium in which to dissect out various parts of the cochlea

If the specimen is to be decalcified it is fixed in the glutaraldehyde fixative for 4 hours and decalcified in EDTA for one week, changing the EDTA daily

The incubation medium is made fresh prior to use and contains: 4 mg 3,3'-diaminobenzidine tetrahydrochloride, 10 ml of 0.07 M Sorensen's buffer and 0.1 ml of 1% H_2O made fresh from 30% H_2O_2 The specimens are incubated in the medium until the desired color of the vessels is achieved. With portions of stria this usually takes 20 minutes, with the organ of Corti 15 minutes and

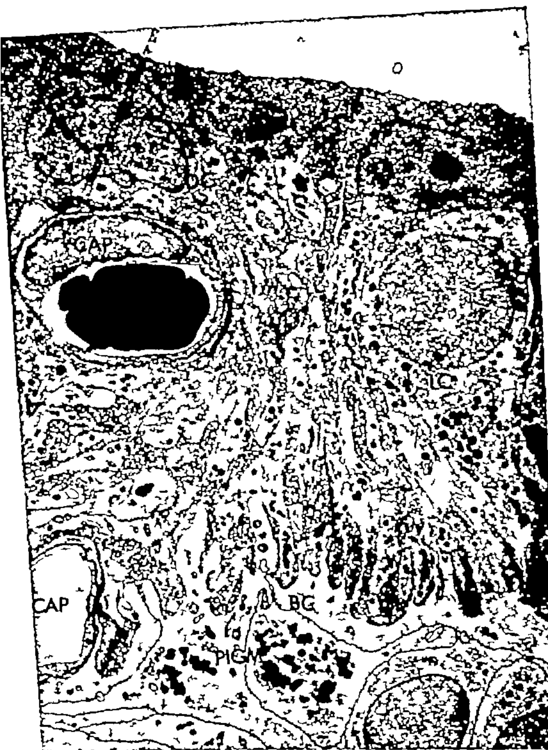


Fig. 3. Electron micrograph from the stria vascularis of a squirrel monkey. There can b seen both dark surface cells (*DC*) and light cells (*LC*) as well as basal cells of connectiv tissue like type. This figure shows the jig-saw-puzzle like interconnection between the thre cell types. There are also seen some blood-vessels (*CAP*) and in some of the cells larg numbers of dark pigment granules. 6 200



Fig 2 A shows the stria vasc laris from the upper and B the stria n the lower portion of the cochlea In these two micrographs two d fferent layers of blood vessel can be seen It also shows that not only the erythrocytes but also the vascular walls are stained (*A*) 325 (B) 345



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if decalcified material is used 1–2 hours. The medium is changed at least every 30 minutes or more often if the color of the solution becomes dark brown. The progress of the reaction is usually observed through a dissecting microscope.

The stria vascularis of squirrel monkeys was prepared for electron microscopy by fixation in glutaraldehyde-osmium or in 1.5% veronal buffered osmic acid for 2 hours at 0–4 C. The specimens were dehydrated in increasing concentrations of alcohol and were embedded in epon. Thin sections were cut on an LKB Ultrotome III with a diamond knife, stained with uranyl acetate and lead hydroxide. The sections were viewed in a Siemens Elmiskop I A electron microscope.

RESULTS

The blood vessels of the lateral cochlear wall are clearly seen with the use of the presently described horseradish peroxidase-benzidine staining technique. The entire vascular anatomy of the external wall of the scala vestibuli, scala media and scala tympani shows a rich pattern of darkly staining vascular channels. In all of our specimens we have observed a consistent and reproducible staining pattern of the vessels in the stria vascularis and the spiral ligament.

In the present report we will only report on some of the more outstanding features of the stria vascularis and the spiral ligament since previous authors have extensively dealt with these topics (Smith, 1954 Axelsson, 1968).

The apical turns are characterized by fewer radiating arterioles and a markedly narrowed stria vascularis (Fig. 1 A) The stria increases in width in the more basal turns Also in the basal coils there are well demarcated spirally running vessels along the stria's inferior and superior borders.

The vessel of the spiral prominence (VSSP) is also a constant feature It is supplied by wide diameter arterioles from the radiating arterioles (Fig. 1 B). Arterio-venous anastomoses (AVAS) are abundantly seen in the spiral ligament (Figs. 1 and 2) These "thorough fare channels appear to be the main network for shunting the blood from the arterial system to the venous circuit. They are also of great importance for the exchange of oxygen and fluid in the spiral ligament

We noted in animals which for control purposes received only saline injection and were processed in the routine manner for demonstrating the vascular channels a rather constant staining of the stria but not of the arteriolar and venous systems These specimens looked very similar to those obtained with the conventional benzidine procedure. The presence of endogenous heme proteins and peroxidase enzymes accounts for this result. However with the addition of injected horseradish peroxidase the results were far more consistant and the quality superior to those without the exogenous enzyme.

In many ways the staining process is like a photographic printing process where the desired darkness of the print may be controlled by the length of time in the developer In the same manner the desired color of the vessels may be



Fig 4 Dark (*DC*) and light (*LC*) cells in the stria of a squirrel monkey. The dark cells contain large numbers of mitochondria in their prolongations. Some pigment (*PIGM*) can be seen. 29 000

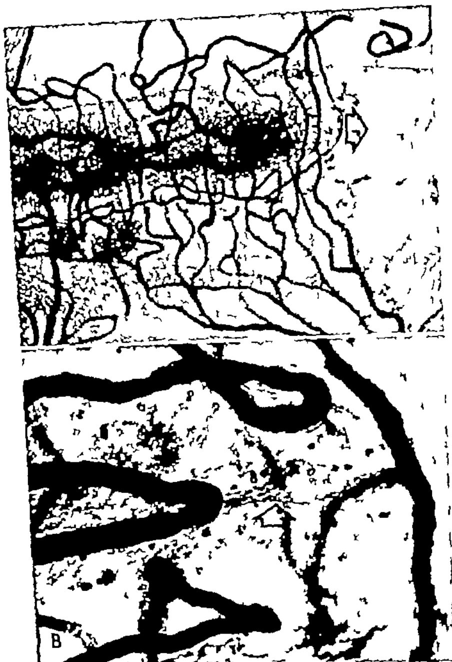
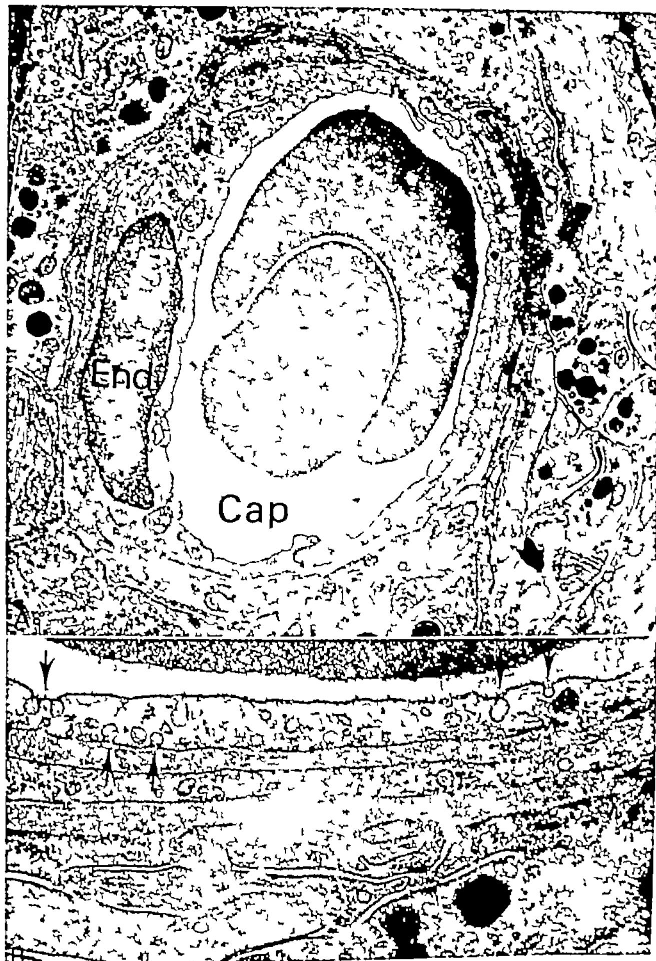


Fig 6 These two striae from guinea pigs are both damaged, A by argon laser irradiation and B by ultrasound. In A the arrow indicates a region of complete destruction of the vascular bed and disappearance of pigment. In B the destruction is complete to the right but some remnants of blood vessels (arrow) indicate where the blood vessels have been. (A) ×165 (B) ×800

Fig 5 (A) Blood vessel (*CAP*) with endothelial cell nucleus (*End*) from the stria of squirrel monkey. On the outside of the vascular wall extensions from dark and light cells. ×25 000. (B) Vascular wall with micropinocytotic vesicles (arrows) in the endothelial cells. ×125 000


End
Cap
A
B

In recent studies Osaka (1971) Winther (1971) and Duvall (1971) have examined the ultrastructural appearance of capillary permeability in the cochlea with particular reference to the stria vascularis. These authors have used a modification of the method introduced for electron microscopy by Karnovsky (1967). It was Strauss (1959) however who introduced the use of intravenously injected horseradish peroxidase as a tracer substance for light microscopy. His extensive studies on the biochemistry of the horseradish peroxidase mediated benzidine reaction have provided a firm theoretical and practical background for the use of this technique in histochemistry.

The basic principle of the technique as used by Strauss, Karnovsky and Duvall and as introduced in this paper for light microscopy of the cochlear vessels is a single enzyme mediated reaction. Horseradish peroxidase is an enzyme (MW 40 000) which acts in catalytic amounts to amplify the basic benzidine reaction. The presence of one molecule of the enzyme can mediate the oxidation of many molecules of benzidine in the presence of H_2O to a blue colored compound which is most likely a salt of a quinhydrone like molecular compound and quinonediamine. The base which forms at high pH is a brown reaction product and is the substance responsible for the staining of the vessels in the present study. Strauss (1964 *a*, *b*) has studied several variables that can affect the formation of a blue reaction product, the effect of pH the concentration of H_2O and benzidine, the time of incubation, the temperature, and the solvent used. Our own studies have shown that the formation of the blue product is not a necessary prerequisite for its effective use in vascular studies of the ear. In fact, because of the intensity of the brown or red-brown reaction product formed at higher pH and its ease of formation, this latter stain is in our opinion and for our purpose more desirable.

The uniqueness of the present method is that the factors which act in the formation of a brown reaction product are the same elements that are necessary to preserve the specimens for further electron microscopic work. The effect of an added water based buffer the physiologic pH range, the temperature and the materials used in fixation all contribute significantly towards good fixation of the tissues for electron microscopy and the optimum formation of the benzidine reaction product. Furthermore the brown color is more stable than the benzidine bl e product and does not require stabilization by nitroprusside as does the latter product. The action of osmium tetroxide on the brown substance is no hindrance in the use of this method.

In our studies we have seen that even without injection of the enzyme the reaction product appears to be found. Although the color and intensity of this reaction is not as sharp as the enzyme mediated one, it is nevertheless a well recognizable phenomenon. We have in fact used this endogeneous reaction much as Smith (1954), Mass (1969) and others to show the vascular supply when it was not possible to inject experimental animals.

The problem with the endogeneous reaction is its dependence upon the presence of erythrocytes. Romeis (1948) in his biochemistry text instructs the investigator

altered by varying the time the specimen is in the incubation medium The presence of the injected enzyme catalyzes the oxidation of many molecules of the diaminobenzidine to the colored reaction product. The appearance of the reaction product is thus not solely dependent upon the filling of the vascular system with erythrocytes. The colored reaction product may be seen inbetween single erythrocytes in the vessel lumen (Fig 1)

Our present efforts have also shown that the injected enzyme is stable to EDTA decalcification but not to nitric acid decalcification We have decalcified over 20 ears using this EDTA method and have subsequently shown the vascular pattern within the bony structures. The incubation time after decalcification is longer but the quality of the resultant reaction product is equal to the stain achieved in nondecalcified specimens

A rather striking feature in our specimens is the large diameter of the capil laries of the stria vascularis (Figs. 1 and 2) These large diameters are dependent upon the time the specimen is stored after incubation. It has been our ex perience that within a few days the physiologic pattern of the stria vascularis is lost and shrinkage of the vessels becomes evident This result has also been noted in other specimens of surface preparation material noteably from the vestibular structures (Rosenhall personal communication) This change may be responsible for the difference in information regarding the dimensions of the stria capillaries in previous reports (Axelsson 1968) and the present one.

The explanation of this fact is of great interest In Axelsson s specimens the interior of the blood vessels only are stained With the present technique not only the blood but also the vascular wall is stained But even if we consider this fact the present technique seems to demonstrate blood vessels with a con siderably larger volume The volume of the stria vessels has important influence on the blood flow Accurate information about the real diameter and volume is necessary The diverging results with different methodology points to an other interesting fact If the different techniques give very great variations there is good reason to believe that the vessels of the stria also intravitally can vary in diameter to a considerable extent This problem has been attacked by some scientists but their results demonstrate only minor variations (Perlman & Kimura 1955 Lawrence 1971)

Our laboratory has been occupied for a long time with studies of the effect of ultrasound and laser on the inner ear It was a logical step to study the present technique in irradiated specimens Stahle and Sugar Sugar et al have started an extensive series of experiments combining these techniques. It has been shown to be easy to damage the stria both by ultrasound and laser and the staining technique has beautifully demonstrated the extent and nature of the damage The stria is affected in different ways depending upon the type of energy and the dose given Ultrasound and laser irradiation (Figs. 6 A and B) cause very interesting patterns of damage in the stria The progress of destruc tion and the persistent appearance of degenerated capillary strands (Fig 6 B) are easily observed by use of the present method

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to completely fill the vascular system for an effective benzidine reaction. In Mass (1969) study he spent considerable surgical time dissecting and occluding the arterial and venous systems. This lengthy procedure may be indicated in some studies but we feel the easier intravenous injection of exogeneous enzyme is preferable. The pseudoperoxidase reaction of Krabisch & Fischel as cited by Mass is both lengthier in its fixation requirements and more time consuming in the incubation process. For these reasons as well as the ease of reproducibility and the preservation of the tissues for electron microscopy we favor the proce dure reported here

The release of histamine by the exogeneous peroxidase enzyme has been studied by Winther (1971) He concluded that in the guinea pig this im munological reaction does not occur Duvall (1971) suggests that the appearance of pores in the stria vascularis and the presence of leukocytes 10 15 minutes after injection of horseradish peroxidase may point to a histamine or serotonin releasing role by the enzyme Cotran & Karnovsky (1967) and Copley & Carol (1964) have also presented data which suggest the guinea pig may release a vasoactive substance after horseradish peroxidase injection Osako (1971) found that injected histamine did not increase the permeability of stria capillaries when 0 1 mg to 0 4 mg was used but found a decreased penetration of reaction product when 2 mg or more was used. It is obvious that Winther s (1971) study which reports no histamine in the blood of horseradish peroxidase injected capil laries is at odds with other reports For our purposes the release of histamine does not seem to be as important as it does in the ultrastructural studies. In terms of quantitative measurements it would be possible to correct for the *histamine effect if it is further documented to occur*

It is hoped that the suggested procedure in the present study will not deter further investigators from modifying the method. Once the basic principles of the histochemistry are understood it is a simple task to adapt this easy reproducible method for any particular problem or experiment. In our own laboratory we are continuing our research into the usefulness of this method and hope that with modification it can be used in cadaver specimens.

SUMMARY

The blood vessels of the lateral cochlear wall in the guinea pig are demonstrated by means of modified benzidine reaction surface preparation technique using in jected horseradish peroxidase The ease and reproducibility of the method is stressed as well as the adaptability of the technique for *various fixatives and* buffers. The new technique is applied to studies of the stria in normal guinea pigs and to striae in animals irradiated by ultrasound and laser In addition some ultrastructural characteristics of the stria of the squirrel monkey are presented

Macula Utriculi and Macula Sacculi in the Squirrel Monkey

by H Engström, B. Bergström[1] and H. W Ades[2]

The vestibular sensory epithelia are recognized as the regions of primary importance for our perception of motion and of our position in space. In normal animals these epithelia react to small gravitational changes and certain of their sensory cells have been regarded for many years as a species of accelerometer Interaction of vision deep sensibility and vestibular function permits us to observe and register accelerations or change of position. In the basic study by Wersäll in 1956 we received the first comprehensive report on the structure of the vestibular epithelia and many later reports have verified his observations The new information on the structure of vestibular sensory cells stimulated further studies on the functional properties of these cells. Lowenstein (1959) and collaborators, Dijkgraaf (1962) Flock (1965) and collaborators (1962) and many others, contributed to the information about the physiological properties of the vestibular sensory cells. An important step in the understanding of the function of the vestibular maculae was the finding of Engström et al. (1962), who first reported a morphological polarization of the macular epithelia. A polarization of crista ampullaris had earlier been described by Lowenstein & Wersall (1959) This was followed by studies by Flock (1964 1967) Spoendlin (1964) Lindeman (1969) and others, showing that the vestibular maculae had a structural as well as a functional polarization. That is, the sensory cells are structurally and functionally oriented in a specific direction over large areas. This polarization changes radically through nearly 180 in the region of the striola (cf Werner 1933 Lindeman, 1969) It has been found further that the striolae and the crests of the cristae have a characteristic population of sensory cells (Lindeman, 1969 Watanuki & Meyer z. Gottesberge 1971)

The vestibular sensory areas are found, one in each of the ampullae of the three semicircular canals, one in the macula sacculi, and one in the macula utriculi They are of fundamental importance for our sense of equilibrium and motion The sensory cells of the vestibular sensory areas are integrated into a functional system for orientation in space and for the perception of linear or angular acceleration. Normally the sensory cells are acted upon by small gravitational forces, but with the development of aircraft and space vehicles, the G forces to which the human vestibular system is exposed have been drastically

[1] Dept of Otolaryngology University of Uppsala, Sweden
[2] Depts of Physiology and Electrical Engineering, Bioacoustics Research Laboratory University of Illinois, Urbana, Illinois, USA

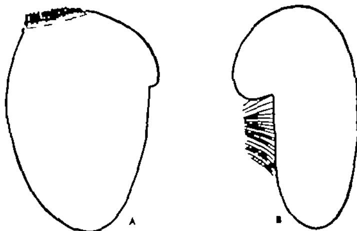


Fig 1 Schematic drawing of (A) macula sacculi and (B) macula utriculi of guinea pig demonstrating the general form of the maculae

as crystals formed postmortem In all our fixed specimens the crystals have been characteristic in form (Fig 2 B) but evidently we have to study living animals to ascertain their true form

Orientation is a result of inputs of information from many receptors in both labyrinths These receptors inform the central nervous system eye muscle nuclei, cerebellum and spinal cord of modifications acting upon the peripheral sensory regions. Feedback systems in the central nervous system actively influence the peripheral sensory cells and nerve fibers. In case of severe damage to the peripheral vestibular system, several of its functional deficits can be compensated for centrally

The form of the maculae in those mammals we have studied (guinea pig, squirrel monkey cat, rabbit, chinchilla, rat) is essentially similar from one species to another They vary in size but have in general the same appearance. The form can be seen in Fig. 1 Our findings are similar to those of Lindeman (1969) though the macula utriculi differs slightly from his. Exceptionally beautiful preparations have been made by Watanuki (1971).

The sensory epithelia of these two maculae differ very little however one important difference is that the orientation of the sensory cells in relation to the striola is reversed This will be discussed further below

The sensory epithelium consists of sensory cells and supporting cells, resting on a basement membrane The maculae are innervated by the saccular nerve and the utricular nerve respectively (cf Lindeman, 1969). The total number of sensory cells on the macula utriculi in man is 33 100 and the total number on the macula sacculi is 18 800 (Rosenhall, 1972) The total number of nerve fibers innervating these is 5 950 for the macula utriculi and 4 050 for the macula sacculi (Bergstrom, in manuscript) They have shown that in man the number of sensory cells as well as the number of nerve fibers is considerably

changed. Unexpected and dramatic reactions may occur during exposure to high or low gravitational forces which has led to an augmentation of interest in the structure and function of the vestibular system Several publications on the morphology of the vestibular sensory epithelia have appeared from our group (Ades & Engström 1965 Engström 1970 Lindeman 1969) The present study which is a direct continuation of our earlier studies on the inner ear has taken up anew the morphology of the sensory regions of one mammal the squirrel monkey The reason for this is evident The development of technique for ultrastructural research has now reached a point at which it is possible to make high quality electron microscopic studies with reproducible results. If we are going to find small alterations in these sensory regions after damage from ototoxic agents or overexposure to G forces, it is imperative to have a detailed background of information on the normal structure. The squirrel monkey has been chosen because it is a commonly used animal and it has an inner ear with a high degree of resemblance to the human inner ear (Spoendlin 1965) We have also used this animal widely in our experiments on the effect of noise or ototoxic agents on inner ear sensory cells.

A large part of this study will be devoted to a photomicrographic documentation of the structure of the vestibular sensory cells and their innervation but attention will also be devoted to a description of the supporting cells. The innervation of the vestibular sensory areas in man has been the subject of a special study by Bergström (in press) who has made a careful quantitative analysis of the number of nerve fibers in the human vestibular nerve. He has found that there is a marked reduction of nerve fibers with increasing age which is in close agreement with the studies by Rosenhall (in press) also of this group who has shown that there is a considerable reduction of sensory cells in the vestibular areas in elderly people Thus, presbyacusis evidently is paralleled by an aging in the vestibular organ

The vestibular labyrinth contains three semicircular canals in each ear with the sensory epithelia on the cristae ampullares, and the utricle and saccule with the sensory cells located respectively in macula utriculi and macula sacculi (Fig. 1) Over the surface of the crista epithelium there is a gelatinous mass, the cupula, with a specific gravity close to that of the endolymph while the maculae have over their surfaces a similar gelatinous mass containing calcite crystals or statoconia (Fig. 2 B) with a specific gravity of approximately 2.74 These crystals have been carefully described by several authors Their composition varies in different species. In mammals they were originally described as composed of aragonite but Brandenberger & Schintz (1945) and Carlström & Engström (1955) proved that mammals have calcite crystals. Lindeman (1969) observed sizes of crystals varying between 1 and 30 μ and he also described a distribution of crystals according to a specific pattern This pattern was verified by Watanuki et al (1971) however Sasaki (1970) was not able to find any large crystals in living animals, but only gel-particles less than 0.1 μ long suspended in a protein solution He regarded the statoconia described above

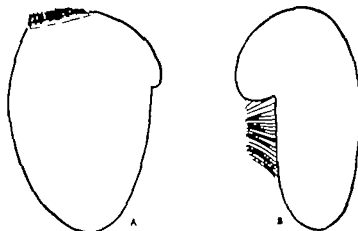


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reduced with increasing age This paper however is concerned principally with the sensory epithelium and its innervation from the standpoint of structure.

As early as 1858 the vestibular sensory epithelia were observed and described by Schulze It remained for Retzius (1884) to describe them further and to make beautiful illustrations of ciliated cells in the epithelium He described cilia of different lengths on individual cells, and his text indicated a recognition that the length difference might be of functional importance

The first thorough description of the vestibular sensory cells waited until Wersäll (1956) was able to accomplish it, using the electron microscope In an extensive study on the structure and innervation of the epithelium of the cristae he described two kinds of sensory cells, type I and type II He further described their innervation and their supporting cells. Wersäll indicated also that the same types of cells could be found in the macular epithelium The principles of organization outlined by Wersäll have been verified by several later observers and little has been added however one important addition has been made and that is the double innervation of all inner ear sensory cells (Engström 1958)

Improvement in instruments and techniques have made possible a more detailed and accurate description of the ultrastructure of the vestibular epithelium A major step was made with the discovery of a structural polarization of the sensory cells on the maculae (Engström et al 1962 Ades et al. 1962 Flock 1964 Spoendlin 1964 Lindeman 1969) In connection with this, an interesting observation was the different structure of the striolar region The striola had already been described by Werner (1933) but his findings were not discussed much before Engström & Wersäll (1958) pointed out that the striolar region of the macula utriculi contains a larger number of the type I cells than do the extra striolar areas. Since then the subdivisions of the vestibular maculae have been carefully studied (cf Lindeman 1969 Watanuki 1972)

In summary then the present concept is that the vestibular maculae consist of receptors of type I and type II surrounded by supporting cells. The epithelium is innervated by myelinated nerves of varying caliber (Bergström in manuscript) There are in addition a fairly large number of non myelinated nerve fibers under the basement membrane (Wersäll 1956 Spoendlin 1965) Whether or not these also enter the sensory epithelium is as yet unknown

The cells of type I (Figs. 3 4 5 6) are flask shaped They have a cuticular surface which is provided with sensory hairs, a narrow neck region and a wider cell body around the nucleus The whole cell with the exception of the uppermost portion is enclosed in a nerve chalice which is the termination of a large caliber myelinated nerve fiber A nerve fiber may form separate chalices around several type I cells or it may form a single larger chalice which encloses several such cells. The chalice is surrounded in turn by supporting cells which extend from the basement membrane to the surface of the macula (Figs. 6, 7)

Each type I cell has a cuticular thickening at its surface (Figs. 7 15 16)



Fig. 2. A shows the general arrangement of the epithelium of macula utriculi in a squirrel monkey. Over the surface sensory hairs of different lengths on individual cells and above the hairs statoconia. B shows the form of the statoconia, hexagonal prisms consisting of calciumcarbonate in the form of calcite. Spec w about ...74.

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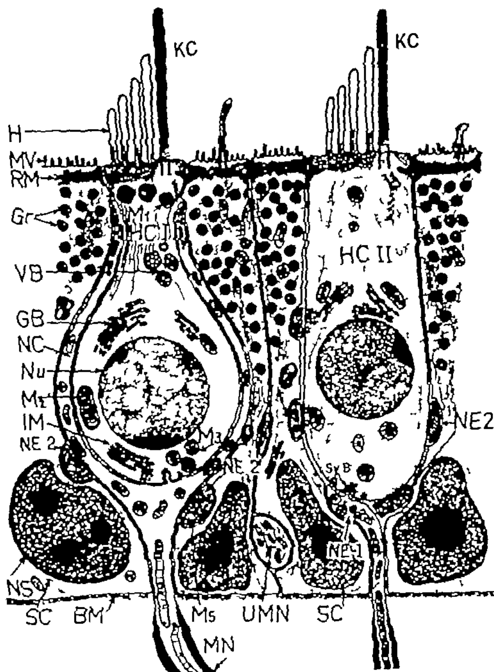


Fig. 3. Schematic drawing of the arrangement of the sensory cells in the vestibular epithelium. This drawing follows in many ways the principles described by Wersäll in 1956. The improved knowledge of the innervation pattern and synaptic structures, of intracellular filaments and of the arrangements of kinocilia on supporting cells should be noticed.

from which protrude a large number of cilia (Fig 16 17) The sensory hairs are of two kinds, one kinocilium and many stereocilia. The kinocilium is usually placed eccentrically with respect both to the stereocilia and the cell s surface (Fig 17 C) but variations on this are seen so that an occasional cell with a centrally located kinocilium is found (Fig. 17 D) The kinocilium is usually the longest of the cilia by a considerable margin. In the squirrel monkey it may have a length of up to 40 μ It is also the thickest of the cilia and the most conspicuous, and is characteristically formed on the well known principle of nine double fibrils surrounding a centrally located pair of fibrils. The central fibrils are not present throughout the whole cilium It is not uncommon to find abnormal kinocilia or double cilia or cilia with many fibrils (Fig 18 A B) Each kinocilium extends from the upper surface of the cell It has a neck portion (Figs. 16 17 B) with a length of about 0 20–0 25 μ and then the kinocilium proper (diameter approximately 0 25–0 30 μ) Inside the cell there is a typical basal body with triple fibers, and from the lower end there extend thin cross-striated fibrils (Spoendlin 1965 Afzelius & Franzén 1971) A centriole can be seen below the basal body (Fig 16) We have often observed that thin non-striated fibrils or tubules extend from the basal body region These fibrils (approximately 230 Å) can be seen in several of our micrographs (Figs 7 8) They extend through the neck portion to the lower part of the cell. Similar fibers have been found in the cochlear hair cells (Ilberg 1969 Engström & Ades, in press) Only the kinocilium is provided with a basal body The stereocilia which are the numerous sensory hairs are inserted with rootlets in the cuticular plate The stereocilia are arranged in regular rows at the surface of the cells (Fig 17 C) Their numbers seem to vary to some extent but they are of the order of 70–80 hairs. They have a varying length with the longest hairs close to the kinocilium gradually tapering off in length away from the kinocilium The gradual decrease in length is quite characteristic As already described the different length of the hairs was seen by Retzius (1884) but it was pointed out anew by Engstrom et al. (1962) The shortest hairs are somewhat thinner than the longer (Fig 17 C) The characteristic arrangement can be seen well in scanning electron microscopy (Engström 1970) The diameter of the thick stereocilia is fairly constant and is about 0 25 μ They have rootlets which almost penetrate the cuticular plate The hair proper having different lengths on the same cell may also differ between different cells This can be seen especially well with the scanning microscope The stereocilia are considerably thinner being 0 10–0 15 μ close to the cuticle The longest kinocilia and stereocilia are found on the ampullar crista while the kinocilia of the macula are usually less than 40 μ Vestigial kinocilia also appear on the supporting cells (Figs. 19 22) but are considerably shorter than those on sensory cells.

The diameter of the surface of the hair cells of type I is approximately 4 μ the thickness of the cuticle may vary but is usually about 1–1.5 μ The region in which the kinocilium is found has no cuticle. The cuticular plate consists of a finely granular or fibrillar material In the periphery of the cuticular

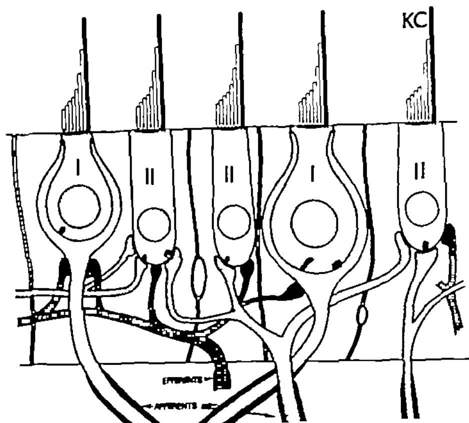


Fig 5 Schematic drawing showing the arrangement of sensory cells and nerve fibers in macula. The myelinated fibers enter the sensory epithelium perpendicularly they pass between the supporting cells and above the nuclear level many fibers form nerve fiber layer parallel with the basement membrane. Some of the thick calibre nerve fibers retain their perpendicular direction to form nerve chalices around type I cells *KC* is kinocilium. The stereocilia by its side are of diminishing lengths in a direction away from the KC.

plate is often found a thin layer of fibrillar nature, with denser lines (Fig. 21 B). It was seen by Friedmann (1968) and later reported by several authors It is said to increase in vestibular sensory cells of man, suffering from Ménière's disease.

The infracuticular region contains a group of mitochondria, each one with a diameter of about 0.35–0.50 μ and a varying length, seldom over 1 μ. The mitochondrial cristae are densely packed. In this region of the type I cell we also find several vesicles or smooth profiles, a poorly developed endoplasmic reticulum with ribosomes, and one to a few multivesiculated bodies on the border of the supranuclear portion. On the border between the cuticle and the infracuticular regions, along the rim of the hair cell is found a ringshaped shelf formed by a reinforcement of high density (Figs. 20 21 and 22). The shelf seems to support the cuticle in such a way that the cuticle rests on and is attached to it The shelf itself is not quite continuous all the way round the cell, and is closely related to the fibrillar structures inside the supporting cells.



Fig 4 Low power electron micrograph of the sensory epithelium of a squirrel monkey I indicates type I cells, II type II cells. NC is the nerve chalice around a type I cell. 4 000



Fig. 7. Upper part of the type I cell in Fig. 7. At this magnification the internal structure of the hair cell and the supporting cells become visible. The nerve chalice contains several mitochondria ... the supporting cells are well developed Golgi complexes (*GB*). The infracuticular mitochondria (*M*) are often found very close to the cuticle of type I cells. × 11 300.



Fig. 6. Typical form of a type I cell in the macula utriculi. The nucleus is slightly irregular. The sensory cell has on its surface sensory hairs (*H*) and it is surrounded by a nerve chalice (*NC*). The complicated arrangement of the reticular membrane (*RM*) is very evident. × 6 200



Fig 7 Upper part of the type I cell in Fig 7 At this magnification the internal structure of the hair cell and the supporting cells become visible The nerve chalice contains several mitochondria I the supporting cells are well developed Golgi complexes (*GB*) The infracuticular mitochondria (*M*) are often found very close to the cuticle of type I cells 11 300.

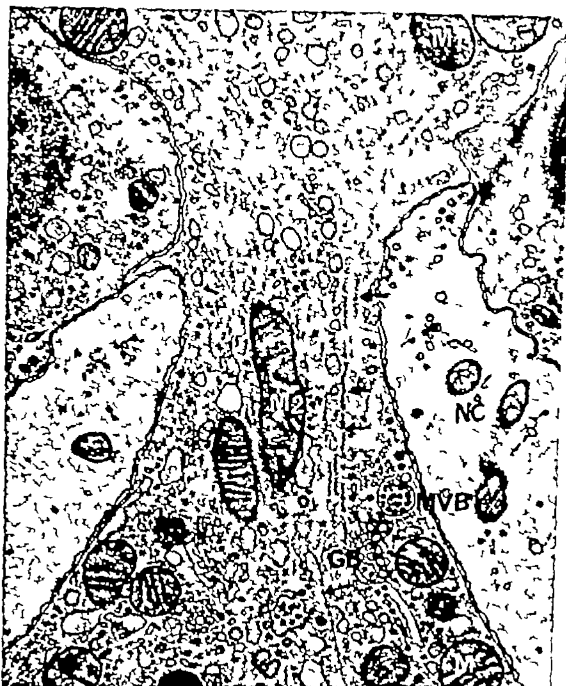


Fig. 8. Supranuclear portion of a type I cell surrounded by the upper part of the nerve chalice (*NC*) which contains a small number of vesicles. In the hair cell M_1 indicates infracuticular and M_2 supranuclear mitochondria. *GB* is a Golgi complex and *MVB* a multivesiculated body. The arrows indicate tubular filaments in the sensory cell. ×5 000



Fig. 9. Base of type I cell surrounded by the nerve chalice (NC). In the nearby supporting cells very thin tonofibrils (F) form distinct fiber system as described by early light microscopists. It can be seen that some nerve fibers (N) run at right angles to the afferent fiber from the nerve chalice. 14 300.



Fig. 10. Type I cell surrounded by its nerve chalice (*NC*) and supporting cells (*SC*). In the supporting cells the tonofibrils can be seen (*F*). The arrows in the lower left corner indicate an efferent nerve ending. × 11 000



Fig. 11. Type I and type II cells near together in the macula utriculi. The type II cells often have their cell bodies "pushed" below or sometimes above the type I cells. I[illegible] this way type II cells may either by very short or [illegible]ery long. [illegible] 3 600



Fig. 12. Lower part of a type II cell and two adjacent type I cells. In the type II cell the white arrows indicate synaptic bars and nearby afferent nerve endings. The type II cells have many bouton-like endings in contact with the cell while only one nerve ending, the chalice, is in contact with type I cells. 6 000



Fig. 13. Lower part of a type II cell from macula utriculi with one afferent (N 1) and one efferent (N 2) nerve ending. Observe the great difference between the mitochondria in the two types. The efferent ending is full of synaptic vesicles. The arrow with a star shows the contact between a type I cell and a nearby nerve chalice. The black arrow shows synaptic vesicles both inside the sensory cell and in the nerve ending. *See also* Fig. 29 E. × 22 000



Fig 12 Lower part of a type II cell and two adjacent type I cells. In the type II cell the white arrows indicate synaptic bars and nearby afferent nerve endings. The type II cells have many bouton-like endings in contact with the cell while only one nerve ending, the chalice is in contact with type I cells. 6 000

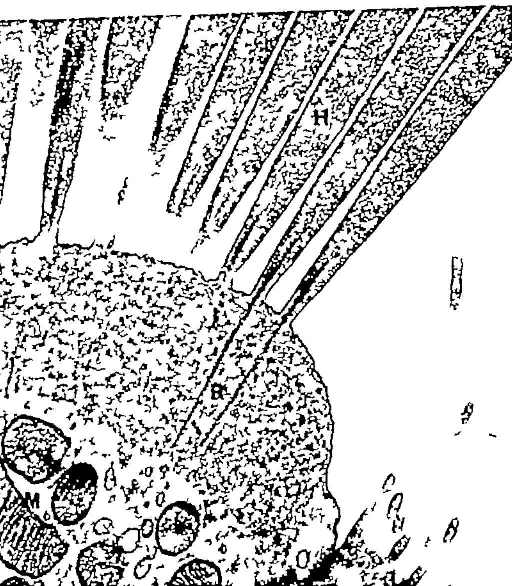


Fig. 15. The cuticular portion of a type I cell in the macula utriculi. From the surface sensory hairs (*H*) protrude. They are thinner close to the cuticle and become thicker peripherally. Each stereocilium has denser central core best seen close to the cuticle and this core continues down into tapering rootlet (*R*) which inserts in the cuticular plate. The infracuticular region contains mitochondria (*M*) with densely packed cristae. × 43 500

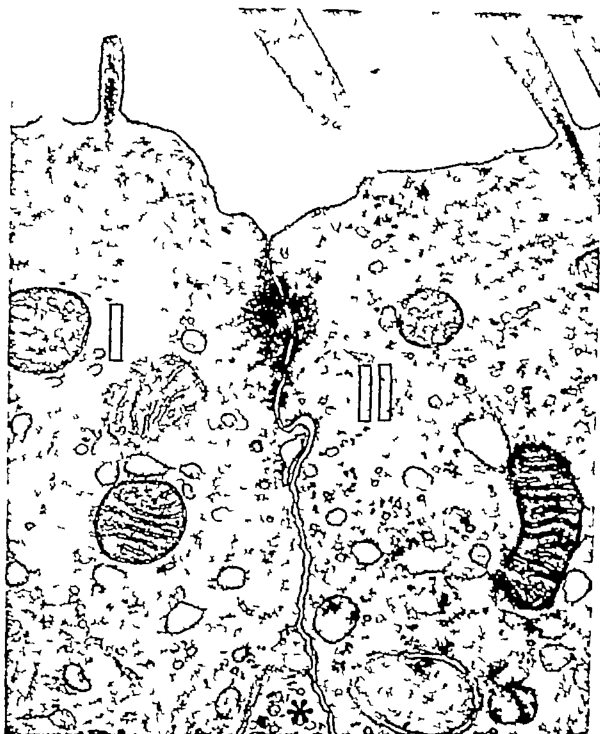


Fig. 14 Type I and type II cells with a small part of a nerve chalice (star). In this case the two cells are bordering directly on each other. The dark area close to th surface f rms a reinforcement in the cells, presumably taking part in the formation of the reticular lamina. 43 500

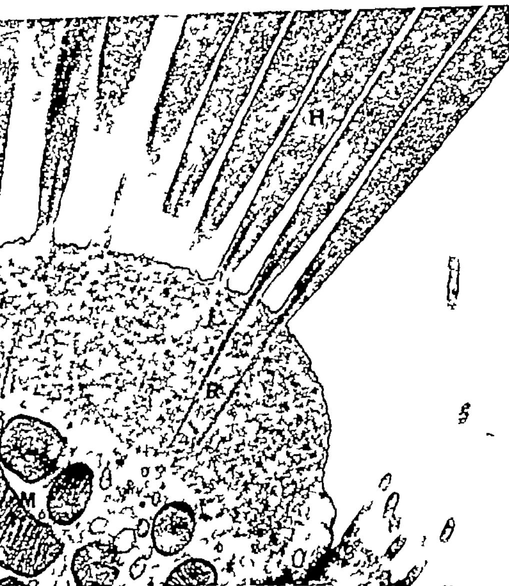


Fig. 15. The cuticular portion of a type I cell in the macula utriculi. From the surface sensory hairs (*H*) protrude. They are thinner close to the cuticle and become thicker peripherally. Each stereocilium has a denser central core best seen close to the cuticle and this core continues down into a tapering rootlet (*R*) which inserts in the cuticular plate. The infracuticular region contains mitochondria (*M*) with densely packed cristae. 43 500.

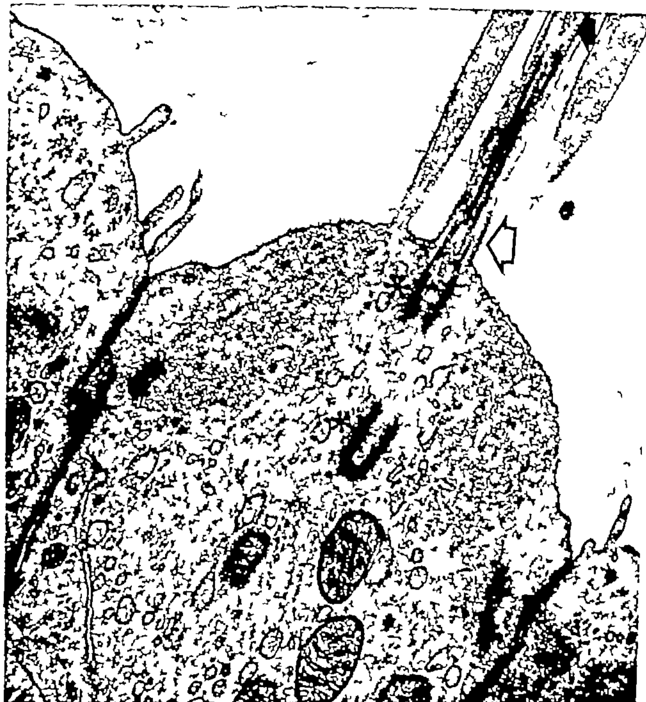


Fig. 16. Type I cell from macula utriculi with one kinocilium and two stereocilia. Below the basal body (star) a centriole (star) can be seen. The open arrow indicates the neck portion of the kinocilium with its spiral structure. The black arrow shows the region in the kinocilium where the central fibrils usually disappear and small granular structures appear. See also Fig. 17 A, B. × 51 000.

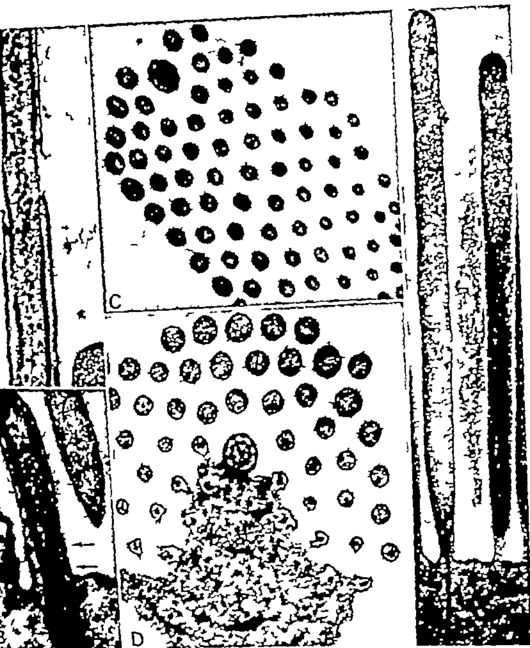


Fig. 17. Different views of kino- and stereocilia from macula utriculi and sacculi. In A and B granules are seen in the center of the kinocilium. In A arrows indicate macromolecular strands often seen in the fixed specimens. In B the arrows indicate the neck portion. C shows the most common arrangement with an eccentrically positioned kinocilium, while D has a central kinocilium. In E some stereocilia are sectioned lengthwise. (A) × 52 500; (B) × 44 000; (C) × 30 000; (D) × 4_ 000; (E) × 33 000.

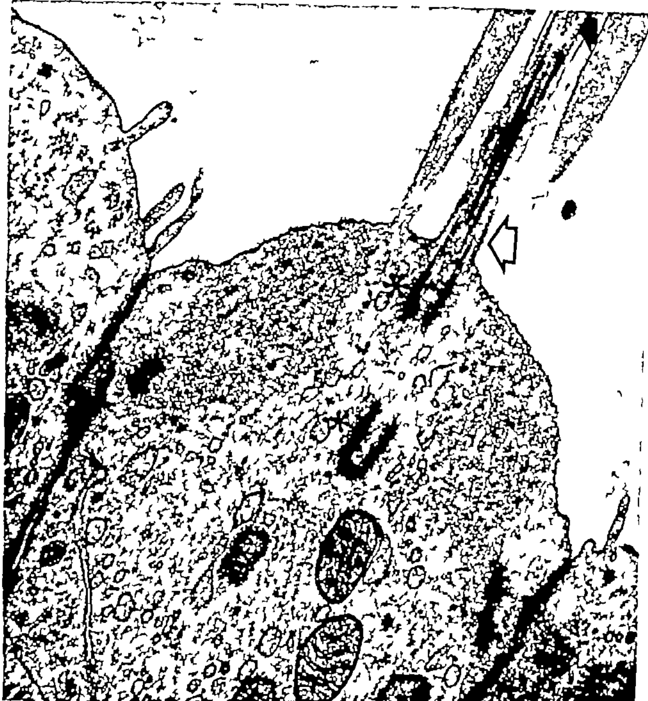


Fig. 16. Type I cell from macula utriculi with one kinocilium and two stereocilia. Below the basal body (star) a centriole (star) can be seen. The open arrow indicates the neck portion of the kinocilium with its spiral structure. The black arrow shows the region in the kinocilium where the central fibrils usually disappear and small granular structures appear. See also Fig. 17 A, B. × 51 000.

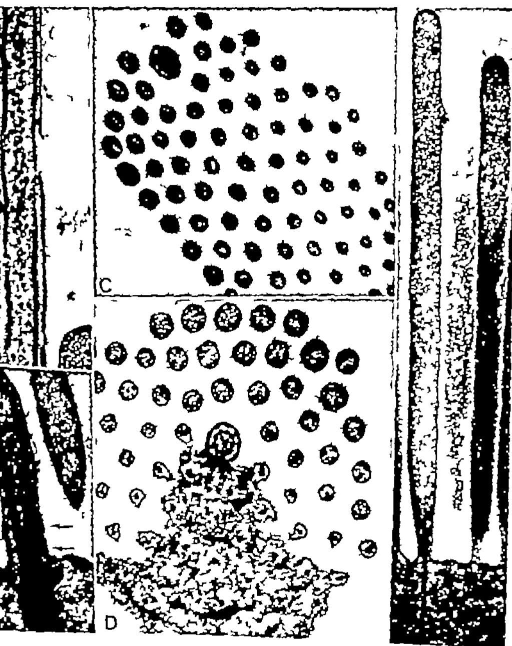


Fig. 17. Different views of kino- and stereocilia from macula utriculi and sacculi. In A and B granules are seen in the center of the kinocilium. In A arrow indicate macro-molecular strands often seen in the fixed specimens. In B the arrows indicate the neck portion. C shows the most common arrangement with an eccentrically positioned kinocilium, while D has central kinocilium. In E some stereocilia are sectioned lengthwise. (A) 52 500 (B) 44 000 (C) 30 000 (D) 42 000 (E) 33 000

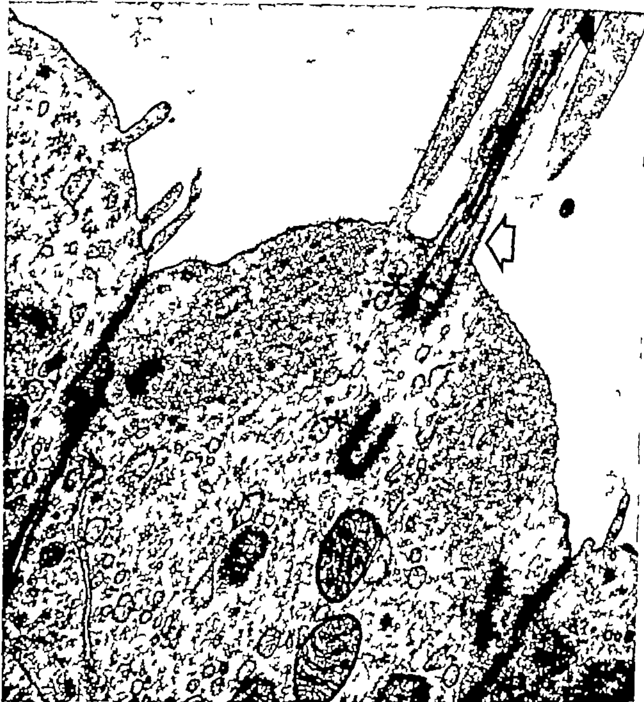


Fig. 16 Type I cell from macula utriculi with one kinocilium and two stereocilia. Below the basal body (star) a centriole (star) can be seen. The open arrow indicates the neck portion of the kinocilium with its spiral structure. The black arrow shows the region in the kinocilium where the central fibrils usually disappear and small granular structures appear. See also Fig. 17 A, B. 51 000



Fig. 19. Section through the surface of macula sacculi. The large and the small black arrow indicate the position of the kinocilia on sensory cells. The open arrow indicates rudimentary kinocilium belonging to supporting cell. Observe the "shelf" formation on the central sensory cell. See also Fig. 20. × 13 000.

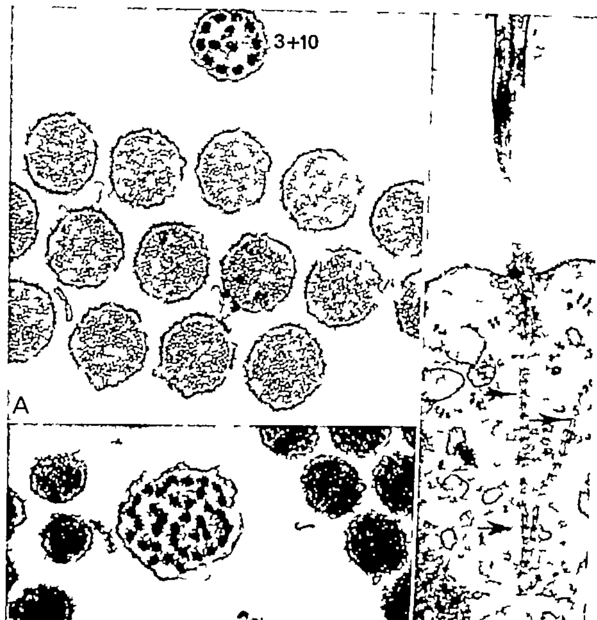


Fig 18 Different views of the cilia on vestibular cells in the squirrel monkey In A are seen a number of stereocilia and one kinocilium In the stereocilia their fibrillar structures (cross-sectioned) can be seen The kinocilium is atypical in so far that it contains 3+10 inner fibrils. 71 000 In B a kinocilium is seen which contains many inner fibrils. 52 000. In C the cross-striated rootfilaments below a kinocilium in a supporting cell is seen. Such filaments have been described by several authors in relation to kinocilia. They are beautifully described by Afzelius and Franzén (1971) in the jellyfish Nausithoe. 39 000



Fig. 19. Section through the surface of macula sacculi. The large and the small black arrows indicate the position of the kinocilia on sensory cells. The open arrow indicates a rudimentary kinocilium belonging to a supporting cell. Observe the "shelf" formation on the central sensory cell. See also Fig. 20. × 13 000.



Fig 20 Sensory cell from macula sacculi cut very close to the cuticle. The arrows indicate a "shelf" formed by a reinforcement in the cell. This irregular shelf is very conspicuous and occurs in relation to the cuticular plate. The impression is that the cuticle rests on the shelf and that it forms an important structure for the stability of the cells. A corresponding structure can be seen in Fig 1 A 30 500



Fig. 21. Sections through the surface of the epithelium of the macula sacculi. In A the large open arrow indicates the shelf described in the text for Fig. 20. The small open arrows indicate rootlets from stereocilia in the cuticular plate. The small dark upper arrow indicates cross-striated rootlets low to the basal body of a supporting cell. The lower dark arrow shows a similar cross-striated structure in a sensory cell. In B the open arrow indicates a cross-striated ribbon-like structure often found in vestibular and sometimes in cochlear sensory cells. It was first noticed by Friedmann et al. and has subsequently been observed by several authors. (A) × 4 000. (B) × 46 500.

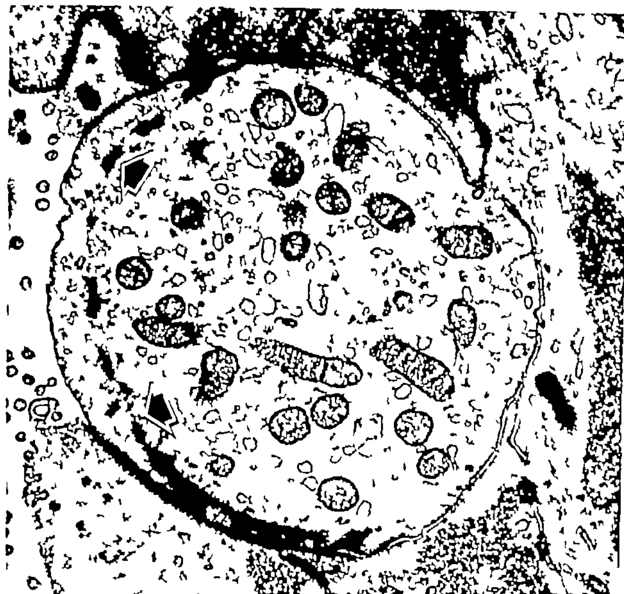


Fig 20 Sensory cell from macula sacculi cut very close to the cuticle The arrows indicate a "shelf" formed by a reinforcement in the cell This irregular shelf is very conspicuous and occurs in relation to the cuticular plate The impression is that the cuticle rests on the shelf and that it forms an important structure for the stability of the cells. A corresponding structure can be seen in Fig. 1 A. 30 500



Fig. 23. A supporting cell (SC) between one type I and one type II cell. The dark matter forming the reticular membrane is very distinct, also the shelf (arrow) in the type I cell. In the type II cell a multivesiculated body (MVB) surrounded by small granules or vesicles can be seen. × 3 000

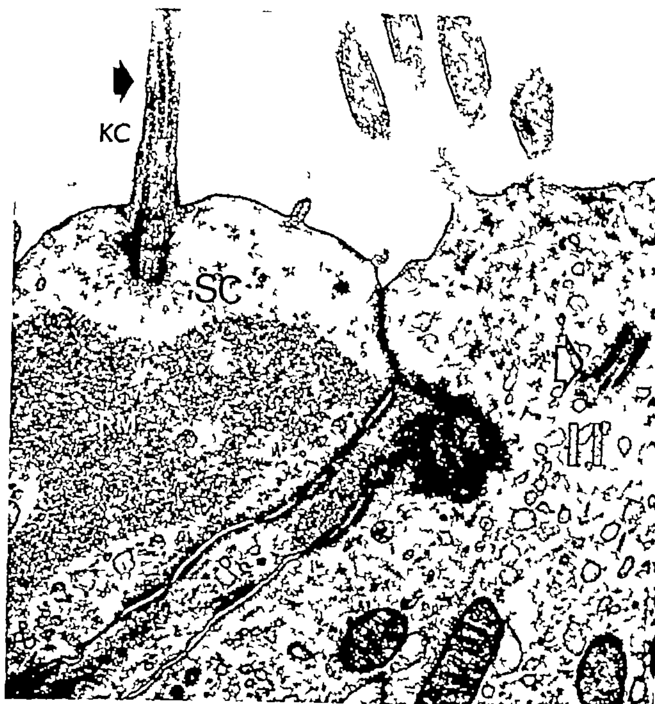


Fig. 22. Supporting cell (*SC*) with a rudimentary kinocilium (*KC*) close to a type II cell (II). The reticular membrane (*RM*) consisting of a very fine fibrillar or granular matter can be seen. In the sensory cell the arrow indicates a centriole below the surface. In the sensory cell the dark "shelf" structure is seen. Observe also the contact between the supporting and the sensory cells. × 39 500.



Fig. 23. A supporting cell (*SC*) between one type I and one type II cell. The dark matter forming the reticular membrane is very distinct, also the shelf (arrow) in the type I cell. I: the type II cell: multivesiculated body (*MVB*) surrounded by small granules or vesicles can be seen. × 32 000.

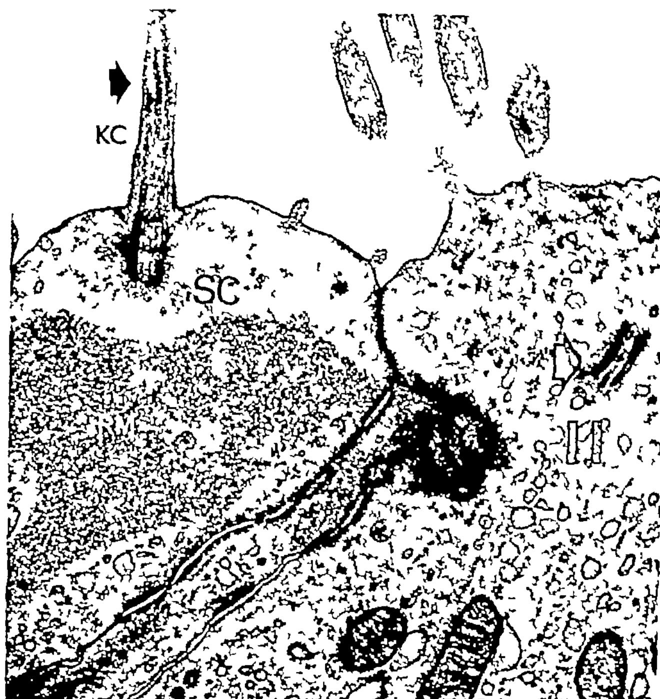


Fig. 2 Supporting cell (*SC*) with a rudimentary kinocilium (*KC*) close to a type II cell (*II*). The reticular membrane (*RM*) consisting of a very fine fibrillar or granular matter can be seen. In the sensory cell the arrow indicates a centriole below the surf ce. In the sensory cell the dark "shelf" structure is seen. Observe also the contact between the supporting and the sensory cells. 39 500



Fig 25 Uppermost portion of a supporting cell From the surface large number of microvilli extend Many of these are cross sectioned and the micro-fibrillar inner structure can be seen. Below the surface there is centriole (*Ce*) in close relation to large number of dark, very thin tonofilaments (dark arrow) Some cross-striated filaments or rootlets (white arrow) are also obvious This micrograph from macula sacculi also shows the interconnection between several supporting cells and one sensory cell Small parts of the reticular membrane are also seen 23 000



Fig. 24 The interconnection between a type II cell and two supporting cells (*SC*). In the cytoplasm of the sensory cell are seen several mitochondria (*M*) and the endoplasmic reticulum. Two adjacent supporting cells are interconnected by a desmosome with minute tonofilaments (dark arrow) which can be followed down into the supporting cells (open arrow). A centriole (*Ce*) is seen in the upper right corner. Macula utriculi. × 45 000



Fig. 25. Uppermost portion of a supporting cell. From the surface large number of microvilli extend. Many of these are cross sectioned and the micro-fibrillar inner structure can be seen. Below the surface there is a centriole (*Ce*) in close relation to large number of dark, very thin tonofilaments (dark arrow). Some cross-striated filaments or rootlets (bare arrow) are also obvious. This micrograph from macula sacculi also shows the interconnection between several supporting cells and one sensory cell. Small parts of the reticular membrane are also seen. 23 000



Fig. 26. Upper portion of a supporting cell with its centriole (arrow) and adjacent endoplasmic reticulum. The dark reticular membrane (*RM*) forms a rather thick layer. At (*De*) the interconnection between three supporting cells is seen. Some granules or vesicles (*V*) are seen. Macula utriculi. × 39 500.



Fig. 27. A shows a sensory cell from macula sacculi cross-sectioned close to the surface. It is surrounded by supporting cells with dense matter belonging to the reticular membrane. The Golgi complex (*GB*) and several multivesiculated bodies (*MVB*) are seen. In B and C Golgi complexes (*GB*) from two supporting cells can be seen. The arrangement of the Golgi complex is well shown in Fig. C. (A) ×25 000 (B) ×45 000 (C) ×35 000



Fig. 26. Upper portion of a supporting cell with its centriole (arrow) and adjacent endoplasmic reticulum. The dark reticular membrane (*RM*) forms a rather thick layer. At (*De*) the interconnection between three supporting cells is seen. Some granules or vesicles (*V*) are seen. Macula utriculi. × 39 500



Fig. 28. Nerve chalice (*NC*) from macula utriculi, with synaptic invagination (*A*), synaptic bar (*B*) and synaptic body (*C*). In the adjacent supporting cell multivesiculated body (*MVB*). × 77 000

Figs. 28 32 The Nerve endings at type I and type II cells are of afferent (*Ne 1*) and efferent (*Ne 2*) nature Around the type I cell in Fig. 28 a nerve chalice (*NC*) is seen The membranes between the sensory cell and the nerve chalice form a regular double line (as seen in Figs. 8 and 29 A C and D) The distance between the two lines has been found (in several measured cells) to vary between 213 1±37.3 Å and 93 1± 9 6 Å At certain levels, usually at the lower end of the type I cell (Fig. 28 white arrow) invaginations may be seen *and these may be rather deep as in Fig. 30 C. In close relation to such invaginations,* where the distance sometimes becomes minimal synaptic bars (Fig 8 B) or synaptic bodies or balls (in Figs 8 29 A B, C and D Fig. 30 A) may be seen These synaptic structures may become very irregular as in 29 D Synaptic bodies or bars are almost always found at afferent synapses but occasionally in serially sectioned specimens we have seen synaptic bodies in relation to richly granulated endings, regarded as of efferent nature (Fig. 9 D) Synaptic bars are found at both type I cells and at type II cells. In the squirrel monkey we have observed synaptic bars with a length of more than 5 μ They are surrounded by synaptic vesicles of the clear type Dense cored vesicles have never been observed by us in the sensory cells.

At many afferent endings at the type II cells irregular infoldings of the plasma membrane of the sensory cells can be seen (Fig. 30 A arrow at *Ne 1 a* Fig 31 A arrows)

At the efferent endings (*Ne 2*) there is often found a subsynaptic cistern (Fig 30 D arrow at *Ne* 2, Fig. 31 B arrow Fig. 3 B arrow) Ribosomes are often seen in relation to the inner membrane of this cistern Only occasionally are subsynaptic cisterns seen in relation to afferent endings (Fig. 30 D *Ne* 1) The efferent synapses contain large numbers of synpatic vesicles of the clear type with a diameter about 230 250 Å The afferent endings contain much fewer vesicles which are very variable in size They range from about 230 Å to more than 1 000 Å Both afferent and efferent endings contain a small number of dense cored vesicles (Fig. 29 B *Ne* 1) These can increase considerably in numb r for instance when the animals have received ototoxic antibiotics.



Fig. 28. Nerve chalice (*NC*) from maculi utriculi, with synaptic invagination (*A*), synaptic bar (*B*) and synaptic body (*C*). In the adjacent supporting cell multivesiculated body (*MVB*). × 27 000

Figs. 28–32 The Nerve endings at type I and type II cells are of afferent (*Ne* 1) and efferent (*Ne* 2) nature. Around the type I cell in Fig. 28 a nerve chalice (*NC*) is seen. The membranes between the sensory cell and the nerve chalice form a regular double line (as seen in Figs 28 and 29 A, C and D). The distance between the two lines has been found (in several *measured cells) to vary between 213.1 ± 37.3 Å and 293.1 ± 29.6 Å*. At certain levels, usually at the lower end of the type I cell (Fig. 28 white arrow) invaginations may be seen and these may be rather deep as in Fig. 30 C. In close relation to such invaginations, where the distance sometimes becomes minimal, synaptic bars (Fig. 28 B) or synaptic bodies or balls (in Figs. 28, 29 A, B, C and D, Fig. 30 A) may be seen. These synaptic structures may become very irregular as in 29 D. Synaptic bodies or bars are almost always found at afferent synapses but occasionally in serially sectioned specimens we have seen synaptic bodies in relation to richly granulated endings, regarded as of efferent nature (Fig. 29 E). Synaptic bars are found at both type I cells and at type II cells. In the squirrel monkey we have observed synaptic bars with a length of more than 5 μ. They are surrounded by synaptic vesicles of the clear type. Dense cored vesicles have never been observed by us in the sensory cells.

At many afferent endings at the type II cells irregular infoldings of the plasma membrane of the sensory cells can be seen (Fig. 30 A, arrow at *Ne 1 a*, Fig. 31 A, arrows).

At the efferent endings (*Ne* 2) there is often found a subsynaptic cistern (Fig. 30 D, arrow at *Ne* 2, Fig. 31 B, arrow, Fig. 32 B, arrow). Ribosomes are often seen in relation to the inner membrane of this cistern. Only occasionally are subsynaptic cisterns seen in relation to afferent endings (Fig. 30 D, *Ne* 1). The efferent synapses contain large numbers of synaptic vesicles of the clear type with a diameter about 230–250 Å. The afferent endings contain much fewer vesicles which are very variable in size. They range from about 230 Å to more than 1 000 Å. Both afferent and efferent endings contain a small number of dense cored vesicles (Fig. 29 B, *Ne* 1). These can increase considerably in number for instance when the animals have received ototoxic antibiotics.



Fig. 28. Nerve chalice (*NC*) from macula utriculi, with synaptic invagination (*A*), synaptic bar (*B*) and synaptic body (*C*). In the adjacent supporting cell multivesiculated body (*MVB*). ×27 000


Ne1
Ne2
D
E



Fig. 30. Different synaptic formations at afferent (N 1) and efferent (N 2) nerve endings. ^ indicate efferent fibers. (A) 31 000. (B and C) magnif. unknown. (D) 60 000.

Fig. 29. (A) Synaptic invagination (arrow) and synaptic body 41 500. (B) Synaptic body or ball (arrow). Dense cored vesicles in afferent ending (N 1) 23 500. (C) Synaptic formations of different kinds 129 000. (D) Irregular synaptic body surrounded by vesicles. 61 000. (E) Synaptic body close to an efferent ending (N 2) 57 500.


Ne
Ne1
Ne2
D
E



Fig. 32. A shows neuro-neuronal synapse (arrow) inside the sensory epithelium of macula utriculi. Observe the large mitochondria in the afferent fibers compared with the mitochondria in *N* 2 in 3. B 29 500. (B) Efferent ending (*N* 2) with adjacent subsynaptic cistern (arrow). This ending is very richly granulated. Diameter of mitochondria about 0.13–0.15 μ. 44 000.



Fig 31 (A) Afferent ending (*Ne* 1) with rich infoldings into the sensory cell formed by *coated invaginations or vesicles (arrows)* 36 000 (*B*) *Efferent ending* (*Ne*) *with a well* developed subsynaptic cistern (arrow). The afferent ending (Ne 1) has a dense synaptic region. 43 000



Fig. 32. A shows neuro-neuronal synapse (arrow) inside the sensory epithelium of macula utriculi. Observe the large mitochondria in the afferent fibers compared with the mitochondria in N in 3 B. ×39 500. (B) Efferent ending (N 2) with adjacent subsynaptic cistern (arrow). This ending is very richly granulated. Diameter of mitochondria about 0.13–0.15 μ. ×44 000.



Fig. 31. (A) Afferent ending (Ne 1) with rich infoldings into the sensory cell formed by coated invaginations or vesicles (arrows). 36 000. (B) Efferent ending (Ne) with a well developed subsynaptic cistern (arrow). The afferent ending (Ne 1) has a dense synaptic region. 43 000


A
G
B

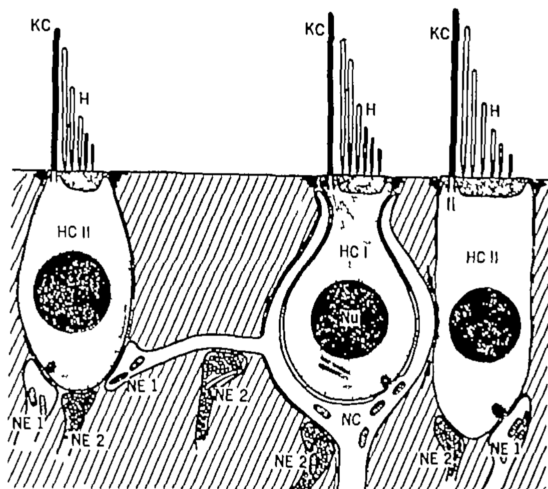


Fig. 33. Schematic drawing of atypical, but not too uncommon innervation in the macular epithelia. The nerve chalice may form synaptic contact not only with a type I cell but also with a type II cell. Occasionally extensions from a nerve chalice may reach and form synaptic contact with a type II cell. The position of the efferent endings may also vary considerably but the principles given in the schematic drawing in Fig. 3 represent the most common forms of innervation.

Fig. 34. In A and B the lower portion of type I cells is seen and the arrows indicate regions where the double membrane between the nerve chalice and the sensory cell has a peculiar appearance. This is in the region of synaptic contact where the membrane has disappeared and granular structures are found instead of the membrane. At first we regarded these formations as preparational artefacts but we have now observed the same kind of structures in many specimens from different animals and different species. The fixation in these cases has been good and many nearby sensory cells show the regular appearance of the membrane as in Figs. 3, 10 and 8. It is very difficult to understand the meaning of this disruption of the synaptic region. We have studied thousands of cells and a tendency to a smaller scale disruption has been observed in many specimens. The extensive disintegration or rearrangement seen in these micrograph has only been found in the squirrel monkey. It is interesting to note that synaptic bars in monkeys are often very long and may extend 5 μ in length. (A) × 9 000, (B) × 40 000.


A
B



Fig. 35

Figs. 35 and 36. These two micrographs represent sections through macula sacculi parallel to the surface about 5 μ above the basement membrane. At this level many afferent nerve fibers (N) run almost horizontally before they turn upwards to the sensory cell. It is common to see branching nerve fibers. The granulated or efferent fibers (N2) are very distinct from the afferent ones. They have much smaller and denser mitochondria and stand out very clearly. In Fig. 36 the appearance of the large mitochondria in the afferent fibers is well shown. All nuclei belong to supporting cells. Fig. 35 × 7 [illegible]00. Fig. 36 × [illegible]0 000.



Fig



F g 37 Myelinated nerve (*MN*) below the bas ment membrane continuing inside the epithelium of macula utriculi. In this case the nerve sheds its myelin just at the basement membrane More commonly the myelin ends some distance from the membrane and only infrequently is myel n seen in the epithelial layer The supporting cells form a distinct layer with their nuclei close to the basement membrane 5 700



Fig. 38.

Figs. 38 and 39. Myelinated nerves shed their myelin below the macular epithelium, as seen in Figs. 37. In Figs. 38 and 39 details are seen of how the myelin unrolls from the axon. The regular layers of myelin form complicated folds and Schwann cell cytoplasm appears within the folds. These formations may be found in large numbers below the macula as described by Engström & Wersäll (1958). Fig. 38 28 000, Fig. 39 (A) 68 000 (B) 73 500



Fig. 37. Myelinated nerve (*MN*) below the basement membrane continuing inside the epithelium of macula utriculi. In this case the nerve sheds its myelin just at the basement membrane. More commonly the myelin ends some distance from the membrane and only infrequently is myelin seen in the epithelial layer. The supporting cells form a distinct layer with their nuclei close to the basement membrane. × 5 700.



Fig 40 Cross sectioned myelinated nerve fibers belonging to the utricular nerve The black arrow indicates Schwann cell cytoplasm containing tubular structures The white arrow indicate unmyelinated nerve fibers I the upper left corner one of these fibers contains dense cored vesicle × 65 000

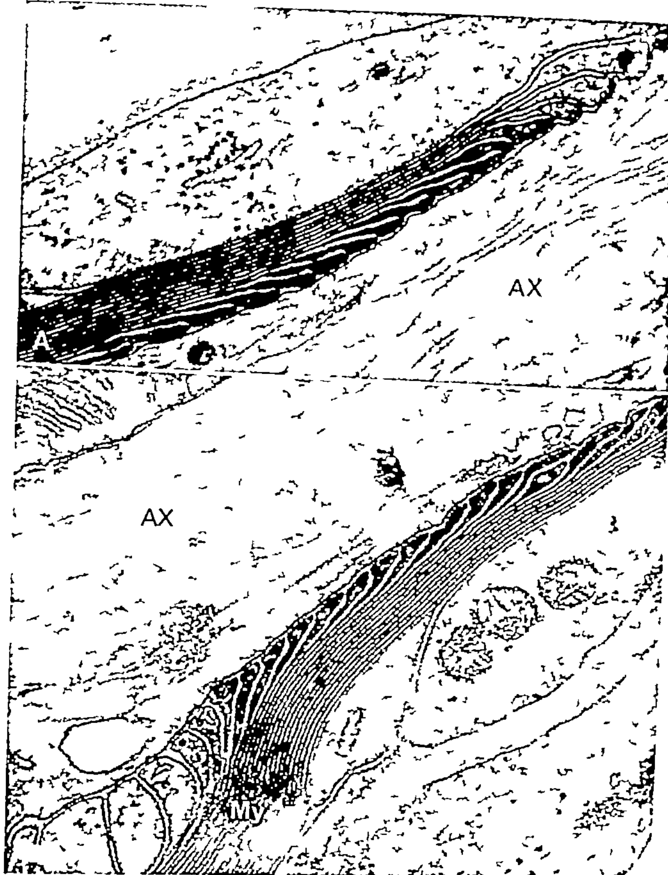


Fig. 39

Table II. *Distance between hair cell and nerve chalice (not synaptic region), type I cell*

Low value	213.1 ± 37.3 Å
High value	293.1 ± 29.6 Å

Distance between sensory cell and nerve ending (synaptic region), type II cell

Afferent	123.0 ± 27.8 Å
Efferent	161.0 ± 18.5 Å

be a little wider in the nuclear region. As can be seen in Fig. 3, they are also provided with stereocilia and one kinocilium. These extend from a cuticle, which is often diffuse and which seems thinner and less dense than the cuticle of type I cells. It seems as though the stereocilia of type I cells spread out more than those of type II cells (Fig. 4).

The infracuticular region and the supranuclear region of type II cells seem to form a more uniform structure than is true for type I cells. There are several mitochondria below the cuticle, but they are distributed into the supranuclear area more than is the case with type I cells. The cytoplasm of these two regions contains more electron dense material, a slightly denser endoplasmic reticulum and more diffusely distributed Golgi complexes. Part of the difference in the type I and type II cells is the difference in distance between surface and nucleus. The infranuclear cytoplasm is similar in the two types of cells. In the long, type II cells the distance from surface to nucleus is often two or three times as large as in type I cells.

The major difference between type I and type II cells otherwise is in their relations to nerve terminals. While the type I cells are almost enclosed in a nerve chalice, the type II cells are innervated by boutons (synaptosomes) or fingerlike endings contacting the plasma membrane in several regions, but mainly in the infranuclear area, however, synaptic contact regions are also found in the supranuclear region (Fig. 12).

The innervation of type I cells is by means of the nerve chalices earlier described. These endings have a very wide area of contact with the sensory cells and this contact differs in structure in different regions. From just below the cuticle, down to the nuclear level, there is a slightly irregular distance between the plasma membrane of the sensory cell and that of the nerve ending. The distance is about 175 Å, but below the nuclear level, it becomes larger and the membranes more regular. The membranes are parallel (Figs. 9, 10, 28) over large distances, and, in certain regions, distinct synaptic areas can be seen. In Figs. 28, 29 and 30 several different synaptic areas can be seen. The intercellular distance has been measured in many places along several cells and it has been found to vary between 213.1 ± 37.3 μ and 293.1 ± 29.6 μ. These measurements can be found in Table II on page 121. In the synaptic regions the distance between the cell membranes is considerably shorter. In some areas invaginations can be seen. The distance can become almost nil in certain areas

Table I *Number of sensory cells in the macula utriculi and sacculi of man according to age* U Rosenhall (in publication)

	Mac. utric.	Mac. saccul
Newborn	32 900	18 400
20–40 yrs	33 400	18 400
80–85 yrs	26 700	14 100

Number of nerve fibers in the vestibular nerve of man according to age B Bergström (unpublished)

	Superior division			Inferior division			
Age	No amp ant. et lat	N utric.	Total	N sacc.	N amp post.	Total	Whole nerve
1 day	5 049	7 203	12 252	3 538	2 983	6 521	18 773
6 weeks	7 985	6 354	14 339	3 749	2 124	5 873	20 212
22 yrs	4 901	5 422	10 323	5 424	2 612	8 036	18 359
78 yrs	3 001	2 599	5 600	1 973	1 701	3 674	9 274
80 yrs	2 618	3 360	5 978	2 784	1 443	4 227	10 205

Fibrillar structures with a diameter of approximately 230 A arise close to the cuticle and the basal body of the kinocilium. The fibrils can be followed through the infracuticular supranuclear perinuclear and infranuclear regions to the vicinity of the nerve endings.

The supranuclear region (Figs. 7 8) contains a well developed endoplasmic reticulum with Golgi complexes, multivesciculated bodies, occasional lysosomes and filamentous structures of the type described earlier

The nucleus is round or ovoid and has a diameter of approximately 6 μ It has a finely granulated chromatine network and a nuclear membrane with many nuclear pores. The nucleolus is seldom prominent Laterally of the nucleus the cellular cytoplasm contains a few mitochondria (diameter approximately 0.5 μ length 2–3 μ)

The infranuclear region (6–7 μ) is the smooth round region below the nucleus. It contains a finely granular cytoplasm with groups of ovoid mitochondria poly ribosomes and a few granulated membranes with ribosomes (Figs. 9 10) At the lower end and along the sides of the infranuclear portion several specialized synaptic regions can be seen.

Almost the whole sensory cell of type I is enclosed in a nerve-chalice which will be described in relation to the innervation of the maculae The synaptic regions will be discussed in relation to this portion of our paper

The sensory cell of type II may vary considerably in length Some cells are quite short only 10–12 μ while others may reach from the surface almost down to the basement membrane In Fig. 4 is seen a type II cell with a length of more than 45 μ The type I cell with a length of 26 μ and another of 33 μ can be seen on either side of it A nearby type II cell is approximately 45 μ long The cells may vary in form also It seems as if the bulging of adjacent type I cells and their nerve chalices push the type II cells downwards and less often upwards Many of the type II cells have a cylindrical form or may

has not shown a corresponding staining either (Iurato et al 1970). The further structure of the calyces will be shown in relation to Figs 9 and 10

The innervation of type II cells differs completely from that of type I cells. The type I cells contact only a single afferent nerve ending while each type II cell contacts several afferent and efferent endings (Figs. 12, 31 A, B and 32 B).

The afferent endings are only sparsely granulated, hence, they appear to have little density in the electron micrograph. They form synaptic contacts with the sensory cells, and several types of synpatic structures can be seen on the side of the sensory cell. They are provided with large mitochondria (0 5–0 9 μ) (Figs. 30 A, 31 A). They contain a few vesicles with varying diameters often amounting to 600–800 Å On the sensory cell side there are synaptic bars, bodies or balls. We have never seen the very long bars observed in type I cells of the squirrel monkey The bars are usually only 0.3–0.5 μ in length. They often arise at a dense synaptic region at the area of contact between nerve ending and sensory cell There is often a coated invagination in the neighborhood as well. All intermediate stages can be seen between bars, bodies and balls, and the synaptic formations also have uniformly sized vesicles on the side of the sensory cell. The vesicles have a diameter of about 230 Å, measured on many vesicles in both utricle and saccule. An exact measurement is difficult as the vesicles are often slightly irregular and not all are cut in the middle The synaptic bodies usually have a diameter of about 0 2–0 3 μ

The efferent endings are richly granulated (Figs. 30 D 31 B) They have smaller mitochondria, of a diameter of 0.15–0.20 μ and they have a different contact with the sensory cells Generally they are filled with synaptic vesicles, of a diameter of about 230 Å. It is possible that some efferent fibers form contacts with afferent fibers also. Close to the synaptic membrane there are no mitochondria but this portion of the efferent ending is full of synaptic vesicles A kind of presynaptic grid close to the synapse can often be seen (cf Engstrom & Ades, 1972) Inside the plasma membrane of the sensory cell there is often a subsynaptic cistern (Fig. 31 B). Such cisterns are particularly well developed in the cochlear hair cells and are a common but not constant finding in these type II cells The efferent endings of type I cells are usually found close to the stem of the nerve calyx. The efferent endings of type II cells are found at several levels from the nucleus downwards. It is extremely difficult to follow in detail the course of the efferent nerve fibres inside the macular epithelia. They run a complicated and richly branching course in the lower part of the sensory epithelium and there is good evidence of "en passant" synapses between efferent nerve fibres both with sensory cells and with afferent fibres.

In the squirrel monkey the nerve fibres inside the macular epithelia are unmyelinated and the myelin sheaths begin directly below the basement membrane as can be seen in Figs. 37–40 Only very occasionally can myelin be found (in infoldings) above the basement membrane In certain fishes myelinated fibres are regularly found in the macular sensory epithelium. The process of

(cf Engström et al 1965) and there is a question whether there is not real fusion of membranes sometimes. Often times the infoldings have no increased density In other cases, they become much darker than the rest of the membrane and not infrequently an infolding becomes a coated invagination possibly developing into a coated vesicle or vesicles (Figs. 30 A B and 31 A) In other regions dense synaptic areas are attached to a synaptic bar or body (Figs. 29 A B C and D) The length of the synaptic bar varies in different animals, some of them being more than 5 μ long Some bars seem to fold or break others have irregular processes ending in condensed dark synaptic formations (Fig 29 D) Flock (personal communication) has seen a beginning synaptic body or ball formation in the side line organ of embryological material and has seen that this bar formation begins near the nucleus. We have no comparable information from our adult monkeys but we have always found synaptic bars and bodies to have close contact with the dense synaptic areas. The synaptic bars, bodies or balls are regularly found at afferent nerve endings however we have seen in a few cases, in serially sectioned material synaptic bodies contacting efferent endings also (Fig 29 E) Vesicles can often be seen inside afferent endings which are usually larger than those in efferent endings. Some dense cored vesicles, usually large ones, can be seen both in afferent and efferent endings. We have not seen dense cored vesicles inside sensory cells. Engström et al (1972) have reported extensive accumulations of dense cored vesicles in the inner spiral bundle of the organ of Corti but we have never observed any comparable accumulations in or beneath the maculae The thickness of the nerve chalices around type I cells diminishes at the nuclear level often to about 0 4 μ The nerve chalice widens toward the stem and the stems may be of different thicknesses. The cytoplasm of the chalice contains mitochondria which are considerably larger than those found in efferent endings. Their diameter is between 0 5–1 μ while those of the efferent endings on the outside of the chalices have a diameter of only 0 15–0 20 μ The efferent mitochondria are also much denser than those found in the chalices. The afferent fibers contain many nerve tubuli and filaments (Figs. 35 and 36) which can be followed high up in the chalices. Smith (1956) reported on vesicles in the uppermost portion of the calyces and this has been verified in the present study She appreciated that these vesicles were of synaptic nature and they have a distinct resemblance to synaptic vesicles. The interesting thing is that if vesicles are of synaptic nature they are usually found on the presynaptic side and the nerve chalice is post synaptic. The synaptic organization at the lower end of the type I cell (Figs 28 29 A and 29 C) is distinctly along the line that the sensory cell contains pre synaptic vesicles around synaptic bars bodies or balls, and the chalice represents the postsynaptic side The nature of the vesicles at the upper margin of the chalices is therefore intriguing but their function is obscure It is interesting to see that in Maillet stained specimens the efferent granulated endings at the base of the chalices stain darkly but we have never found that the rims of the chalices take up the color in a similar way Acetylcholine esterase staining

ZUSAMMENFASSUNG

In der Arbeit wird eine Übersicht über die Struktur der Sinnesepithelien in der Macula sacculi und Macula utriculi von Saimiri Sciureus (squirrel monkey) gegeben.

Die Verfasser haben eine systematische Untersuchung von der Form und Ultrastruktur der Sinneszellen und ihren Stützzellen gemacht und beschreiben auch genau die Innervation der Sinneszellen von sowohl Typus I als auch Typus II (nach Wersäll).

Die Arbeit wird von einer grossen Anzahl Mikrophotographien begleitet und besonderen Wert wurde auf bildliche Präsentation der Sinnesepithelien gelegt.

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The supporting cells in the maculae reach from the basement membrane to the surface of the epithelium They have a very irregular form and their nuclei are almost always found just above the basement membrane and below the sensory cells. The irregular form of the supporting cells is caused by their location between the sensory cells. At the surface they separate the individual sensory cells which are usually surrounded by a "ring" of supporting cells. This has been beautifully demonstrated by Lindeman (1969) and by Watanuki (1972) The nuclei of the cells are ovoid with the chromatin frequently lying in clusters centrally but also at the periphery The cytoplasm contains many cytoplasmic organelles as can be seen in many of the micrographs. There are often well developed Golgi complexes, many mitochondria and occasional lipid droplets. The upper part of the supporting cell contains large numbers of round or ovoid granules often with ribosomes along their surface. The nature of these granules is not yet clear

The surface of the supporting cells is covered with a moderate number of microvilli of a varying length sometimes almost 1 μ long These microvilli seem to be attached in some way to the gelatinous matter found above the surface The surface portion of the supporting cells contains a dense material which takes part in the formation of the reticular membrane This membrane has a very typical appearance (Lindeman 1969 Watanuki 1971 1972) The individual bars are very irregular as can be seen in many of our micrographs.

It has been repeatedly described in older literature that the supporting cells contain supporting filaments but this could not be well documented by electron microscopy In the present study it has regularly been observed that the supporting cells contain very thin fibrillar structures forming a reinforcing structure within the cells. These fibrils reach from the base of the cells close to the surface where they seem to integrate with the thin filament found in the desmosomes (Figs. 9 and 10)

SUMMARY

This study provides a description of the sensory epithelium of the maculae utriculi and sacculi in the squirrel monkey Particular interest has been devoted to a description of the ultrastructure of the maculae.

The study contains a large number of transmission electron micrographs and also some scanning electron micrographs and schematic drawings. Special attention has been given to the innervation of the sensory cells The sensory cells are of two distinct types named types I and II according to Wersäll Their structure and innervation is very different and many of these details can be seen in the micrographs A series of micrographs demonstrate the myelinization region of the afferent nerve fibres.

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SUPPLEMENT 303

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WAYNE O OLSEN, PH.D.,

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From the Auditory Research Laboratories,
Department of Otolaryngology and Maxillofacial Surgery
Vestibular Research Laboratory Department of Otolaryngology
and Maxillofacial Surgery and Department of Neurology
Physical Medicine and Rehabilitation,
Northwestern University, McGaw Medical Center
Chicago, Illinois, USA

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From the Auditory Research Laboratories,
Department of Otolaryngology and Maxillofacial Surgery
Vestibular Research Laboratory Department of Otolaryngology
and Maxillofacial Surgery and Department of Neurology
Physical Medicine and Rehabilitation,
Northwestern University McGaw Medical Center
Chicago, Illinois, USA

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Abstract

This supplement presents audiological, vestibular and neurological data collected from 61 persons with multiple sclerosis. These persons were administered an extensive battery of tests in each of the aforementioned areas in an effort to learn more about the function of the human central auditory and vestibular nervous systems. Auditory and vestibular findings were analyzed in relation to neurological involvements of the low brainstem high brainstem, midbrain and cortical levels as inferred from the neurological examination Attention was also given to the implications to be drawn from the test results in light of the fact that multiple sclerosis is a disease of the central nervous system.

The neurological evaluation consisted of history taking, examination of clinical laboratory and medical reports (available for all patients), and a thorough clinical neurological examination by the project's neurologist. From such procedures and other special procedures when needed sites of lesions were inferred by the project neurologist in terms of four general levels of the central nervous system These inferred levels of damage were considered during analysis of the auditory and vestibular data

The auditory test battery consisted of routine pure tone and speech threshold testing, the establishment of discrimination ability for monosyllables, and of a series of special tonal and speech tests The 6 special tonal tests included tests of adaptation, loudness function, and short increment sensitivity as well as 3 tests of binaural auditory function

The 4 speech tests included discrimination of words in the presence of ipsilateral white noise, versus a contralateral competing speech message, in various filtered modes, and in various binaural masking situations.

The vestibular evaluation employed 4 main procedures, namely a group of tests concerned with visually induced eye movements, a check for spontaneous nystagmus, a search for positional nystagmus, and a look at response to caloric stimulation. All of the evaluation was conducted utilizing electronystagmographic techniques.

The results were considered individually and in terms of incidence of patterns of results. Generally neurological evaluation of the 61 subjects revealed symptoms suggesting multileveled lesions of the central nervous system, particularly in the midbrain and brainstem. Auditory evaluations demonstrated a marked diversity of auditory aberrations which were most commonly elicited by tests requiring response to a sustained stimulus, by tests requiring discrimination of speech in conditions other than quiet, and by binaural masking tests. Vestibular evaluations showed a similar variety of noteworthy results. Abnormal visually induced eye movements, positional nystagmus, and hyper excitability in response to caloric stimulation were the most common findings.

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1 Background to the Study

I. INTRODUCTION

A review of the literature reveals a diversity of auditory behavior associated with multiple sclerosis. This diversity is not unexpected when one recalls that multiple sclerosis is a fluctuating, albeit basically progressive disease of the central nervous system wherein the site(s) of the lesion(s) varies from one patient to the next.

Given this variability the study of auditory dysfunction due to multiple sclerosis in conjunction with neurological evaluations can increase one's insight into normal and abnormal auditory function in two ways. First, administration of a battery of special auditory tests can provide additional information about how multiple sclerosis patients perform on these tests and the types of disruption of normal auditory function to be expected. Second, correlation of auditory test results with the clinically inferred sites of lesion which are provided by competent neurologists can help increase one's understanding of the relationship between lesions of the central nervous system and breakdowns in hearing ability.

The present paper reviews the auditory aberrations of a fairly large group of patients with multiple sclerosis. The paper also analyzes the relation between these aberrations and neurological signs exhibited by these patients. Vestibular findings on some of the patients are also reported. Before embarking upon these discussions, however, a brief review of some key aspects of multiple sclerosis is pertinent.

II. NATURE OF MULTIPLE SCLEROSIS

Multiple sclerosis is one of the most common degenerative diseases of the central nervous system found throughout the temperate zone. It is characterized clinically by remissions and relapses occurring over a period of months-to-years, with the signs and symptoms reflecting patchy involvement of the neural axis. Although the disease is pleomorphic in its presentation, its pathologic lesions, referred to as "plaques" are confined to the white matter of the brain, brainstem, and spinal cord. The cerebral lesions are frequently seen in the paraventricular areas, especially in relation to the lateral ventricles. In the brainstem, the lesions are often present around the third and fourth ventricle. In the spinal cord, the lesions are confined to the white matter and do not extend beyond the root entry zone. Another area of predilection is the optic nerve. It has been estimated that about 40% of patients with multiple sclerosis suffer from optic neuritis. The most common brainstem and midbrain signs include incoordination nystagmus, diplopia and/or the medial longitudinal fasciculus (MLF) syndrome.

The histopathological characteristics of the plaques are quite typical, and the loss of myelin with preservation of the axon is fundamental to the lesion. In addition, the younger lesions demonstrate mono-nuclear infiltration, oligodendroglial degeneration, and microglial reaction. The older lesions show *fibrous* astrocytic reaction. Perivascular reaction and edema are also quite characteristic of the lesions. During active phases of the disease, cerebrospinal fluid shows pleocytosis, normal or elevated total protein, and a significant rise in gamma globulin fraction.

III. VESTIBULAR INVOLVEMENT

It has long been well recognized that patients with multiple sclerosis may report vertigo or

dizziness as one of their complaints, sometimes, although rarely as the presenting symptom Multiple sclerosis patients often exhibit nystagmus, with a reported incidence of 5 to 57 (Leidler 1917 Mygind, 1933 von Leden & Horton 1948 Bentzen et al. 1951 Hallberg, 1956 Cannizzaro 1957 Salonna & Carbonara 1959 Parker et al 1962 Citron et al 1963 Preibish-Effenberger 1963 Rose & Daly 1964 Dayal et al. 1966 Rataj & Mizske 1966 Collard et al., 1969) Dissociated and ataxic nystagmus have been commonly found in multiple sclerosis patients (e.g., von Leden & Horton, 1948 Parker et al 1962) and was thought pathognomonic of multiple sclerosis by Harris (1944) Spontaneous and/or lateral gaze nystagmus were exhibited by patients with multiple sclerosis reported by Hallberg (1956) Citron et al (1963) Dayal et al (1966) and Collard et al (1969) These varieties of nystagmus as well as the dizziness and unsteadiness often described by multiple sclerosis patients are probably due to foci of demyelination which may occur anywhere from the cerebellum and root of the VIIIth nerve up through the remainder of the central vestibular system (Leidler 1917 Ward et al 1965)

IV AUDITORY INVOLVEMENT

Auditory symptomatology though recognized is not completely understood and there appears to be no agreement in the literature as to the nature of hearing loss in multiple sclerosis Leidler (1917) described his findings in 13 patients with multiple sclerosis who came to autopsy All had nystagmus and he particularly searched for damage within the vestibular system His examination extended from the end organ to the ocular nuclei and included the cerebellum he found much of this area susceptible to disruption by multiple sclerosis The plaques ranged in size from flecks within bundles of ascending fibers to massive lesions that had largely demyelinated the brainstem. Findings in the auditory system were similarly diverse Lesions were noted to involve the VIIIth nerve the cochlear nuclei the trapezoid complex, and the higher nuclear centers and pathways. In one case for example, a large plaque occupied a portion of the pons and medulla The acoustic nerve was attacked on one side at its insertion to the pons and was mostly encompassed by the plaque throughout the pons and medulla. The lateral lemniscus, however was free of demyelination On the other side sclerotic foci were confined to the region of the vestibular nuclei and the floor of the fourth ventricle

Brock & Gagel (1933) reported the case of a 25 year old male who died two months after the onset of what proved to be acute multiple sclerosis At the time of death the patient had a bilaterally severe hearing loss (by forks and subjectively) which had paralleled in severity the progression of the disease process. Autopsy revealed a large plaque in the area of the right ventral cochlear nucleus near the VIIIth nerve entrance. Other plaques were found bilaterally in the medulla at the level of the superior olives which affected the vagal and glossopharyngeal nuclei The absence of glial cells suggested a recent disease process.

Dix (1968) described a 70 year old male who died three months after onset of an episode much like the one reported by Brock & Gagel Included in the symptomatology were ataxia, slurred speech slight nystagmus in both directions, and clumsiness of the right arm and leg Palsies of cranial nerves III–XII and signs of cerebellar damage were present on the right side Despite the widespread cranial nerve signs vestibular abnormalities appeared slight

Auditory tests revealed a severe hearing loss in the right ear characterized by a drop-off to no hearing by 4 000 Hz The left ear had only a slight high frequency loss Fowler s alternate binaural loudness balance test demonstrated an absence of recruitment at 1 000 Hz and decruitment at 500 and 2 000 Hz. Discomfort levels for pure tones were sought and the findings, according to Dix confirmed the lack of recruitment in the right ear

At post mortem examination sectioning of the brainstem revealed a grey plaque which Dix

judged as probably being due to multiple sclerosis. The plaque occupied an area near the right inferior cerebellar peduncle. At the level of the insertion of the VIIIth auditory nerve to the brainstem, the plaque encompassed a large area including the dorsal and ventral cochlear nuclei, the trapezoid body and the VIIIth nerve fibres near the cochlear nuclei. Overall, nearly two-thirds of the right half of the brainstem was damaged at this level. The estibular nuclei however were largely spared. These histological findings are of particular interest in view of the hearing impairment in this case.

Many different suggestions about type and site of lesion have been offered to explain the auditory aberrations present in some cases of multiple sclerosis. Such diversity probably is attributable to the episodic nature of the disease and to the various test procedures used by investigators in evaluating the auditory function of patients with multiple sclerosis. Mygind (1933) concluded that since multiple sclerotic patients usually had bass deafness, the cause of such deafness must be a "choked labyrinth" rather than "neuritis or nuclear damage. He did acknowledge, however that auditory behavior in some persons with multiple sclerosis mimicked that of cases with VIIIth nerve tumor. Hallpike (1967) claimed that "... the lesions of multiple sclerosis are confined to the central nervous system. They may occur in the cranial nerves, but are then restricted to the zone of the so-called glial protrusion which is correctly regarded as an extension of the central nervous system" (p. 493).

Fisch (1970) pointed out that the VIIIth nerve "... has two distinct segments which differ histologically. The central part has the histological character of fiber tracts within the brain substance (that is, the endoneurium and the neurilemmal sheath are missing and the supporting tissue consists of glial cells). The peripheral part has the appearance of a peripheral nerve" (p. 102). He also stated that "... the *glial* portion of the auditory nerve which traverses the subarachnoid space, is more vulnerable to injury by toxic or infectious influences than the peripheral portion and is also more vulnerable when compared to other cranial nerves" (p. 102).

Multiple sclerosis is known to affect nervous tissue supported by glial cells, such that one would logically expect to find multiple sclerosis plaques involving the glial portion of the VIIIth nerve. Skinner (1929) stated that the point of junction of the peripheral and central parts of the auditory nerve varies in its distance from the middle cerebellar peduncle from 10 to 13 mm in the human male and from 7 to 10 mm in the female. This junction is frequently more distal in the "... vestibular than in the cochlear nerve ... (and) is in most instances within the porus acousticus" (Nager 1969 p. 252).

Citron et al. (1963) specifically assigned the auditory damage in multiple sclerosis to the VIIIth nerve between the spiral ganglia and the insertion of the nerve trunk into the cochlear nucleus. Similar placement of damage was inferred by Hennebert (1966) and by Rose & Daly (1964) on the basis of marked tone decay and on the demonstrable reversibility of such decay and of the pure tone loss. They suggested that the remissive nature of the symptoms was attributable to either a *reversible* demyelination or a perimyelinic edema, i.e. an edemic pressure on the nerve which occurred only during active stages of the disease. Sakamoto & Ichiro (1968) reported excessive adaptation from 2 multiple sclerotic patients during Bekesy audiometry thus indicating the possibility of VIIIth nerve lesion. Antonelli & DeMitri (1963) suggested that when hearing loss is demonstrable for pure tones, the lesion involves the VIIIth nerve or cochlear nucleus. Further they stated, in cases whose only auditory dysfunction is restricted to special speech tests, the damage probably lies at higher regions of the central auditory system. Parker et al. (1962) speculated that hearing impairment due to multiple sclerosis results from damage to "second order neurons". Damage at higher levels, especially within the pons and midbrain, was suggested by Rataj & Mischke (1966) and by Kehajov (1965, 1967).

Ward, Cannon & Lindsay (1965), after con-

sidering much of the speculation just cited con cluded that The loci of the lesions responsible for auditory vestibular and cranial nerve signs and symptoms have generally been attributed to lesions encroaching on the brainstem nuclei and their suprasegmental or intersegmental pathways rather than the peripheral nerves Several reports contained authenticated cases of true involvement of the nerve roots by plaque-like lesions. Close scrutiny (of this evidence) suggested that the lesions were direct extensions of dorsal lateral brainstem plaques that did not extend into the peripheral nerve proper (p 1035) After review of the pertinent literature, including Leidler s (1917) autopsy population Ward et al concluded "In our review no well documented evidence of multiple sclerosis involving peripheral or cranial nerves, beyond the region where the nerve trunk enters the central nervous system, was found" (p 1035)

There is no agreement in the literature regard ing the incidence and types of hearing impair ment associated with multiple sclerosis Many reports of hearing loss for pure tones have appeared (Dundas-Grant, 1921–22 von Leden & Horton 1948 Bentzen et al., 1951 Salonna & Carbonara 1959 Simpkins, 1961 Antonelli & DeMitri 1963 Preibish Effenberger 1963 Ivers & Goldstein 1963 Rose & Daly 1964 Kehajov 1965 Ravenna, 1965 Dayal et al 1966 LeZak & Selhub 1966 Dayal & Swisher 1967 Kehajov 1967 Shulga 1967 Taniewski & Kugler 1967 Parker et al 1968 Sakamoto & Ichiro 1968 Williams 1968 Conraux & Collard 1969 and Dayal et al 1970) The studies mentioned above described population sizes from 2 364 multiple sclerotic patients and incidences of pure tone loss from 1–86 %. Most commonly however incidence of hearing loss was about 50 Almost every possible audiometric configuration was noted but mild high frequency losses were most common Collard et al (1969) claimed that the mild nature of the pure tone loss was characteristic of multiple sclerosis. Highfrequency hearing loss was also most prevalent in case studies reported by Hallberg (1956) Cannizzaro (1957) Parker et al (1962) Citron et al (1963) and Rataj & Mizle (1966) Sopek & Sipowicz (1969) however described a transitory unilateral low frequency hearing loss in 1 case

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V SUMMARY

The foregoing review makes clear the fact that multiple sclerotic lesions vary from case to case and, in a single individual, from time to time. It also highlights the fact that multiple sclerosis disturbs auditory behavior in some instances and that the resulting symptomatology is diverse.

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Research Laboratory (Medical School Branch). Whenever possible, all the tests reported below were administered, but special considerations in individual cases made it impossible always to do so. The number of times each test was given is reported in the results chapter. What follows in this section is a description of the several auditory tests and the rationale for including each one.

A. Pure tone audiometry

The evaluation started with conventional discrete frequency pure tone audiometry. This basic test provided data on subjects' hearing sensitivity across the frequency range from 125–8 000 Hz, on air-bone relationships in cases of loss in hearing sensitivity, and on the configuration of impairment. Comparison of this configuration with the contours of loss generally associated with various auditory diseases allowed identification of instances where the auditory system had been coincidentally damaged by causes other than multiple sclerosis. In instances which exhibited such coincidental effects, the task was to estimate (from all the data at hand) the degree and configuration of hearing loss attributable to multiple sclerosis. One of the goals was to avoid assigning to multiple sclerosis any pure tone deficits which it had not produced. Fortunately, since multiple sclerosis strikes most often in the young adult years, complicating coincidental pathology was absent in most cases.

B. Speech audiometry

Traditional measures of speech reception threshold (for spondees) and intelligibility of monosyllabic words [NU 6 version presented at 40 dB re SRT (Tillman & Carhart, 1966)] were obtained. These and all other speech test materials were stored on magnetic tape. Later 4 other speech tests were administered. In the first 3 of these discrimination of monosyllables had to be made under more difficult listening conditions. In the fourth, spondees were the test items.

One test consisted of monosyllables (NU 6 version at 40 dB re SRT) presented monaurally and simultaneously with white noise. The S/N ratio was 0 dB. Dayal et al. (1966) found that 9 of 13 multiple sclerotic patients so tested experienced substantial breakdown in discrimination when they presented monosyllables in white noise at an S/N ratio of +10 dB. In our laboratory most normals score from 70 to 80 % correct on this test. It has been our clinical experience that some persons with peripheral (cochlear or VIIIth nerve) involvements experience substantial difficulty with this test even though their speech discrimination in quiet for the test materials is excellent (90–100 %). Discrimination of monosyllables in the presence of white noise also has been found to be substantially decreased in some patients with surgically confirmed temporal lobe lesions (Sinha, 1959).

A second test was designed to search for lesions at the brainstem level. It was a modification of the Matzker (1959) filtered speech test. NU6 monosyllables were recorded synchronously on 2 channels of a magnetic tape with pass-bands of 250–750 Hz on channel 1 and 1250–1750 Hz on channel 2. When normals were asked to integrate the 2 channels at a sensation level of +26 dB re SRT they scored about 80 % correct irrespective of whether both channels were presented to 1 ear or 1 was administered via the right ear and the other via the left ear or vice versa. Breakdown on this test is generally accepted as being a clue to involvement of the auditory system in the brainstem (Matzker, 1959). Preibish-Effenberger (1963) gave a Matzker-type test to 50 subjects with multiple sclerosis and found that ... of them did not integrate the 2 channels normally.

The third special speech test employed competing messages. This test consisted of presentation of NU6 monosyllables at 50 dB SL to 1 ear while competing sentences were administered at 60 dB SL to the other ear. It is an easy listening task for most persons except for those with involvement of the auditory system at the cortical level. The usual score for normal hearers is between 90 and 100 %. In other words, a listener can keep the two trains of stimuli iso-

2 Investigative Plan

I INTRODUCTION

The heterogeneity of past findings regarding the auditory responses of multiple sclerosis patients is undoubtedly due partly to differences in the sites and extents of lesions produced by the disease and partly to the variety of hearing tests employed by past investigators This situation prompted the present study Its goal was to obtain auditory neurological, and vestibular data concurrently so that relations between breakdown in hearing function and inferred site of lesion could be traced ante mortem

To this end neurological information was gathered from each patient s case record and a special neurological examination was administered to many of the patients during the study itself Every patient received a series of preselected audiological tests Many of the patients also received a standardized vestibular examination The auditory and vestibular tests were usually performed on the same day in the laboratories of the Department of Otolaryngology and Maxillofacial Surgery Northwestern University Medical School The neurological examination was given in the same location within a day or two

II SUBJECTS

In this investigation 61 patients with multiple sclerosis were studied These individuals ranged in age from 20–64 years (with a mean age of 41 years) Thirty five were female and 26 were male Most of them were drawn from the Northwestern University Multiple Sclerosis Clinic and the remainder from referrals by private physicians Some patients have been tested more than once. In such instances, only the latest set of results on each patient is presented here

III NEUROLOGICAL EVALUATION

Neurological information was available for each of the cases reviewed here In a few instances, the neurological information was taken from case histories, hospital charts, or information provided by the referring physician All the other subjects received medical and neurological examinations at the Northwestern University Multiple Sclerosis Clinic and/or by Dr Vinod Sahgal, who was the neurologist participating in this study The neurological and other medical data on every patient were subsequently analyzed by Dr Sahgal He designated the foci where he inferred from the information at hand, that the patient possessed sclerotic lesions. These judgments regarding the location and extent of neural pathology were used later for evaluation of the auditory and vestibular findings that emerged from the study The neurological examination and inquiry were conducted in accordance with the format used in the collaborative study on the effects of ACTH on multiple sclerosis (Rose et al 1970) Briefly in this format a comprehensive history of the patient s symptomatology and medical background is obtained In addition checks are made of visual acuity and field abnormalities, of deep tendon and pathologic reflexes and of cranial nerve function Limb weakness, spasticity and coordination are explored Sensory deficits (vibratory position pain and touch) are also sought. Tests of gait are completed when possible Further examinations were completed as deemed necessary by Dr Sahgal

IV AUDIOLOGICAL EVALUATION

Each patient was given a battery of hearing tests in the Northwestern University Auditory

Research Laboratory (Medical School Branch). Whenever possible, all the tests reported below were administered, but special considerations in individual cases made it impossible always to do so. The number of times each test was given is reported in the results chapter. What follows in this section is a description of the several auditory tests and the rationale for including each one.

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Traditional measures of speech reception threshold (for spondees) and intelligibility of monosyllabic words [NU 6 version presented at 40 dB re SRT (Tillman & Carhart, 1966)] were obtained. These and all other speech test materials were stored on magnetic tape. Later 4 other speech tests were administered. In the first 3 of these, discrimination of monosyllables had to be made under more difficult listening conditions. In the fourth, spondees were the test items.

One test consisted of monosyllables (NU 6 version at 40 dB re SRT) presented monaurally and simultaneously with white noise. The S/N ratio was 0 dB. Dayal et al. (1966) found that 9 of 13 multiple sclerotic patients so tested experienced substantial breakdown in discrimination when they presented monosyllables in white noise at an S/N ratio of +10 dB. In our laboratory most normals score from 70 to 80% correct on this test. It has been our clinical experience that some persons with peripheral (cochlear or VIIIth nerve) involvements experience substantial difficulty with this test even though their speech discrimination in quiet for the test materials is excellent (90–100%). Discrimination of monosyllables in the presence of white noise also has been found to be substantially decreased in some patients with surgically confirmed temporal lobe lesions (Sinha, 1959).

A second test was designed to search for lesions at the brainstem level. It was a modification of the Matzker (1959) filtered speech test. NU6 monosyllables were recorded synchronously on 2 channels of a magnetic tape with pass-bands of 250–750 Hz on channel 1 and 1250–1750 Hz on channel 2. When normals were asked to integrate the 2 channels at a sensation level of +26 dB re SRT they scored about 80% correct irrespective of whether both channels were presented to 1 ear or 1 was administered via the right ear and the other via the left ear or vice versa. Breakdown on this test is generally accepted as being a clue to involvement of the auditory system in the brainstem (Matzker 1959). Preibish-Effenberger (1963) gave a Matzker-type test to 50 subjects with multiple sclerosis and found that 22 of them did not integrate the 2 channels normally.

The third special speech test employed competing messages. This test consisted of presentation of NU6 monosyllables at 50 dB SL to 1 ear while competing sentences were administered at 60 dB SL to the other ear. It is an easy listening task for most persons except for those with involvement of the auditory system at the cortical level. The usual score for normal hearers is between 90 and 100%. In other words, a listener can keep the two trains of stimuli iso-

2 Investigative Plan

I INTRODUCTION

The heterogeneity of past findings regarding the auditory responses of multiple sclerosis patients is undoubtedly due partly to differences in the sites and extents of lesions produced by the disease and partly to the variety of hearing tests employed by past investigators This situation prompted the present study Its goal was to obtain auditory neurological and vestibular data concurrently so that relations between breakdown in hearing function and inferred site of lesion could be traced ante mortem

To this end neurological information was gathered from each patient s case record and a special neurological examination was administered to many of the patients during the study itself Every patient received a series of preselected audiological tests Many of the patients also received a standardized vestibular examination The auditory and vestibular tests were usually performed on the same day in the laboratories of the Department of Otolaryngology and Maxillofacial Surgery Northwestern University Medical School The neurological examination was given in the same location within a day or two

II SUBJECTS

In this investigation 61 patients with multiple sclerosis were studied These individuals ranged in age from 20–64 years (with a mean age of 41 years) Thirty five were female and 26 were male Most of them were drawn from the Northwestern University Multiple Sclerosis Clinic and the remainder from referrals by private physicians Some patients have been tested more than once In such instances, only the latest set of results on each patient is presented here

III NEUROLOGICAL EVALUATION

Neurological information was available for each of the cases reviewed here In a few instances the neurological information was taken from case histories hospital charts or information provided by the referring physician All the other subjects received medical and neurological examinations at the Northwestern University Multiple Sclerosis Clinic and/or by Dr Vinod Sahgal who was the neurologist participating in this study The neurological and other medical data on every patient were subsequently analyzed by Dr Sahgal He designated the foci where he inferred from the information at hand that the patient possessed sclerotic lesions These judgments regarding the location and extent of neural pathology were used later for evaluation of the auditory and vestibular findings that emerged from the study The neurological examination and inquiry were conducted in accordance with the format used in the collaborative study on the effects of ACTH on multiple sclerosis (Rose et al 1970) Briefly in this format a comprehensive history of the patient s symptomatology and medical background is obtained In addition checks are made of visual acuity and field abnormalities, of deep tendon and pathologic reflexes and of cranial nerve function Limb weakness, spasticity and coordination are explored Sensory deficits (vibratory position pain and touch) are also sought Tests of gait are completed when possible Further examinations were completed as deemed necessary by Dr Sahgal

IV AUDIOLOGICAL EVALUATION

Each patient was given a battery of hearing tests in the Northwestern University Auditory

excessively slow i.e., decruitment (Davis & Goodman, 1966). Recruitment, as defined in the auditory literature, describes a condition in which loudness growth in an impaired ear is considerably more rapid than in a companion normal ear. Decruitment, on the other hand, labels a situation in which thresholds are similar and normal bilaterally but in which at supra threshold levels, loudness experience is decreased in one ear as compared to the opposite ear.

The fifth special tonal test was the simultaneous binaural median plane localization (SBMPL) test. This test examines the lateralization capacity of the subject (de Bruine-Altes, 1946). The basic procedure of the SBMPL test is to present the same pure tone to both ears in phase and to vary the intensity of the stimulus to one ear until a fused image is perceived in the midline. The critical point is that the auditory system must be relatively intact within the brainstem in order for perceptual fusion (and hence lateralization) of the two stimuli to occur. A few isolated reports in the literature (e.g. Jerger 1960*b*) indicate that persons with brainstem lesions affecting the auditory system cannot achieve fusion. The typical manifestation in such instances is dramatic breakdown in the ability to localize the stimulus image.

The last special tonal test measured masking level differences (MLDs) for 500 Hz. The procedure employed was basically the same as used for the speech MLD test. The binaural threshold for 500 Hz in the presence of an 80 dB SPL narrow band noise centered at 500 Hz was obtained during homophasic presentation (both signals in phase interaurally) and during antiphasic reception (the tone out of phase and the noise in phase interaurally). The improvement in sensitivity resulting from transition to the antiphasic condition is the pure tone MLD. MLD phenomena have been extensively studied with normal subjects and sophisticated theories regarding the binaural mechanisms at work have been formulated (Durlach, 1963. Jeffress, 1965. Schenkel, 1967). With our test procedure (Bekesy tracking for the masked thresholds), 95 of the persons in a large sample of normal hearers attained MLDs of 8 dB or greater with the mean 500 Hz MLD being 11.2 dB. Schoeny & Carhart (1971) found that MLDs for 500 Hz exhibited by patients with unilateral Menière's disease were reduced. They thus demonstrated that end-organ involvement on one side when matched with normal hearing on the other can somewhat disrupt the escape from masking which yields MLDs. No one has taken the next step, namely to ascertain how much MLDs for tones or speech are disrupted in persons with bilaterally normal sensitivity for pure tones and speech, but with central involvement. The present study represents an initial step in that direction.

V. VESTIBULAR EVALUATION

The functioning of the vestibular system of 44 of the 61 multiple sclerotic patients was examined by means of electronystagmography (ENG). A preselected sequence of tests was administered in the Vestibular Research Laboratory at Northwestern University Medical School under the guidance of one of the authors (Dr Cecil Hart) who also interpreted all of the resulting data.

A. Visually induced eye movements

The reasons for including tests of visually induced eye movements in the ENG examination were two. First, unless the visual and oculomotor systems were functioning normally analysis of the vestibulo-ocular reflex, as measured at the eye, might be open to error. Also much useful clinical information may be derived from a study of the visual and oculo-motor systems and of the vestibulo-ocular reflex since their function may be subject to a variety of modifications by various neurological mechanisms throughout their paths. Such information is particularly likely to appear in multiple sclerosis, where oculo-motor disturbances are encountered frequently. The following is a description of the tests for visually induced eye movements routinely carried out during the study.

lated from one another Tests of this type have been found useful in evaluating central auditory disorders (Jerger 1964) Breakdown in performance when it did occur was characterized by disruption of performance via the ear opposite the cortical lesion.

The last special speech test measured the masking level difference (MLD) for spondees (Carhart Tillman & Johnson 1966 Carhart Tillman & Dallos, 1968) Spondee thresholds in the presence of broad band noise at 80 dB SPL were determined under 2 binaural listening conditions The first was homophasic. Here both the noise and the speech were in phase with themselves at the 2 ears (S_oN_o) The second condition was antiphasic, i e., each word was now out of phase with itself at the two ears ($S_\pi N_o$) The MLD is the improvement in masked threshold observed during antiphasic listening. Under our test conditions the mean spondee MLD for normal hearers is 8 7 dB and 95 % achieve spondee MLDs of 6 or more dB The speech MLD test has not been used clinically but it was included in the present study because its outcome clearly depends on the adequacy of binaural neurological interactions which are central

C. Special pure tone tests

A series of 6 special tonal tests was also used

One of these was Carhart's (1957) threshold tone decay test. It was usually administered at 500 1 000 2 000 4 000 and 8 000 Hz. Normal behavior on the Carhart tone decay test is characterized by very little tone decay (Willeford 1960) Patients with end-organ lesion may perform similarly or may exhibit up to 30 dB of adaptation at higher frequencies Persons with active VIIIth nerve pathologies (Tillman 1969) and with brainstem lesions (Parker et al 1968) often exhibit adaptation much in excess of 30 dB A variation of the test measured tonal perversion i e., tone to-noise decay rather than tonal disappearance. Both phenomena were sought since Parker et al (1968) have demonstrated that some persons with multiple sclerosis show hyperadaptation of one type while others experience the second type

The second tonal test was Békésy audiometry (Jerger 1960*a* Owens, 1964) Fixed frequency threshold tracings of up to 3 minutes duration were obtained at 500 1 000 2 000 4 000, and 8 000 Hz. The relationship between the tracings for interrupted and continuous tones was used to assign each set of data to 1 of the 4 categories described by Jerger It will be recalled that the Type II pattern is most characteristic of cochlear lesions, while Types III and IV usually emerge when there are active VIIIth nerve lesions. The Type I configuration is ordinarily interpreted as resulting when both cochlear and VIIIth nerve functions are normal. Thus, the Type I pattern is expected both when there is no problem whatsoever and in some forms of central auditory involvement. However Parker et al (1968) have obtained Type III and Type IV tracings from patients with brainstem involvement.

The SISI test (Jerger et al., 1959) was administered at 1 000 2 000 and 4 000 Hz. It was utilized to assess the ability of the listener to detect small changes in stimulus intensity at 20 dB SL and at 85 dB HL. Positive SISI results, scores of 60% or higher obtained at 20 dB SL, are conventionally interpreted as an indication of cochlear involvement when there is sensorineural loss. Under similar circumstances, SISI scores of 30% or less are construed to denote retrocochlear involvement. Similarly low scores are expected from normal hearers or from persons with very mild hearing losses. If the SISI test is administered at 85 dB HL in such instances, high scores result Failure to obtain high scores under these circumstances has been found in cases of VIIIth nerve involvement Such findings are particularly striking when an individual fails to respond to increments of 2–5 dB during the SISI test at either of the presentation levels (Thompson 1963)

Fowler's alternate binaural loudness balance test [ABLB (Fowler 1928)] was given at 500 1 000 and 4 000 Hz. This test provides information about the loudness function of the auditory system i e whether growth in loudness is normal excessively rapid i e recruitment or

excessively slow i.e., decruitment (Davis & Goodman, 1966). Recruitment, as defined in the auditory literature, describes a condition in which loudness growth in an impaired ear is considerably more rapid than in a companion normal ear. Decruitment, on the other hand, labels a situation in which thresholds are similar and normal bilaterally but in which at supra-threshold levels, loudness experience is decreased in one ear as compared to the opposite ear.

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Fig 1a Absence of any baseline shift on opening and closing the eyes.



Fig 1b An example of (abnormal) baseline shift (35° to the left) on closing the eyes.

1 *Lateral gaze imbalance*

The test is performed by seating the patient erect in a chair and having him gaze at a marker on the wall in the direct line of vision The patient alternately opens and closes his eyes, and the ENG record is examined for a consistent sustained shift to one side or the other Examples of normal and abnormal test results are shown in Figs. 1*a* and *b* In a similar test, Cogan (1948) found a deviation to occur in only 2% of normal subjects Patients with cerebral lesions showed an incidence of 72%, and a deviation was found in 84% of patients with brainstem and cerebellar lesions.

Although disturbances in lateral gaze may possibly occur at the level of the cortex the basal ganglia and the superior colliculi the major control of lateral gaze is probably at the level of the pons The so-called pontine center for conjugate lateral gaze is probably in the vicinity of the abducens nuclei for which reason it is sometimes called the parabducens center (Cogan 1956 Crosby 1953)

Cortical and labyrinthine control of lateral gaze is apparently also mediated through the centers in the vestibular nuclei concerned with horizontal gaze Thus a unilateral or asymmetrical lesion of any of these pathways or centers, either destructive or irritative, may upset the balance between the two systems and result in an imbalance in the centering mechanisms of the eye

Once the eyes are closed and the fixation reflex is eliminated, the eyes are free to adopt their resting position. Under normal circumstances the electrical ENG position should be midline, the Bell's phenomenon cancelling out bilaterally However if there is an imbalance between the 2 halves of the pathways and centers discussed above the eyes, and thus their common electrical axis, may come to rest off-center to some degree.

2. *Slow pursuit*

The test of slow pursuit movements is accomplished by requesting the patient to follow a black vertical stripe as it moves across his field of vision, first in 1 direction and then in the other inducing an eye speed of 5°/sec. An example of the record which results is shown in Fig. 2*a* Pursuit movement abnormalities in multiple sclerosis have been documented by Henriksson et al (1969) and by von Noorden & Preziosi (1966) An example of abnormal pursuit is shown in Fig 2*b*

3 *Pendulum tracking*

The patient is again seated erect and while keeping the head still follows with his eyes the motion of a pendulum suspended from the ceiling. The pendulum has an arc of about 30° as subtended from the patient's eyes, at a distance of about 3 meters, with an average frequency of about 4 cycles per second This task again repre-



Fig 2a. An example of normal pursuit eye movements (5°/sec).



Fig 2b. An example of abnormal pursuit eye movements (5°/sec).



Fig. 3a. An example of normal pendulum tracking.



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sents a pursuit eye movement, although somewhat faster than the slow pursuit movement described above Instead of being a pursuit at a constant velocity this test involves a constantly changing velocity of the eye, with reversal of direction at each half cycle.

In discussing abnormal pursuit ("step-wise" pursuit recordings), von Noorden & Preziosi (1966) reported finding this phenomenon in a selection of patients with various disease processes, all of which involved the cerebellum. For this reason, they associated this sign fairly specifically with cerebellar disease Abnormal pursuit can be seen in many conditions, including Wilson s disease (Goldberg & von Noorden, 1966), strabismic amblyopia (on Noorden & Preziosi 1966), myotonic dystrophy (von Noorden, 1969), and brain concussion and cerebellopontine angle tumors (von Noorden & Preziosi, 1966) An example of normal pendulum tracking is shown in Fig 3*a* and abnormal tracking in Fig 3*b*

Abnormalities of pendulum tracking in patients with multiple sclerosis were first noticed by Cords in 1930 He found such abnormalities in 34 of his patients (18/60). This phenomenon also has been found by von Noorden & Preziosi (1966) in 66 of their patients (10/15), and by Benitez (1970) in 78 of his patients (54/69)

4 *Optokinetic nystagmus*

This test is performed ith the patient seated erect and watching a large optokinetic drum with a diameter of 30 inches which is directly in the line of gaze and at a distance of about 3 feet. The drum itself is white, with thin black vertical lines. The drum is rotated, first in one direction, and then in the other such that the eye speed induced should be 20 per second. Examples of a normal and an abnormal trace are given in Figs. 4*a* and *b*

Disturbances of optokinetic nystagmus may occur as a result of a variety of lesions, including damage to the pons and brainstem, areas which are quite frequently involved in multiple sclerosis. Cogan (1956) stated that " lesions of the cerebellum and brainstem may produce disturbances of optokinetic nystagmus on one side, but the defective response is usually bilateral " (p 201).

B. Spontaneous nystagmus

The second major procedure of the vestibular study involved a search for spontaneous nystagmus. A variety of nystagmic patterns may be seen in multiple sclerosis. The nystagmus may be either unidirectional or may change in direction with change in the direction of gaze (gaze nystagmus) The fast phase in this instance is usually in the direction of the deviation of the eye.

Pathological gaze nystagmus is commonly seen with lesions of the cerebellum and sometimes of the brainstem. It is quite often "fixation dependent" and may be either attenuated or totally eliminated by the application of Frenzel s

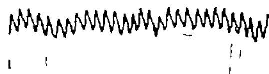


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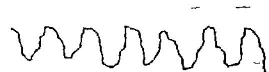


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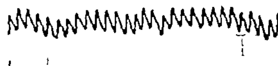


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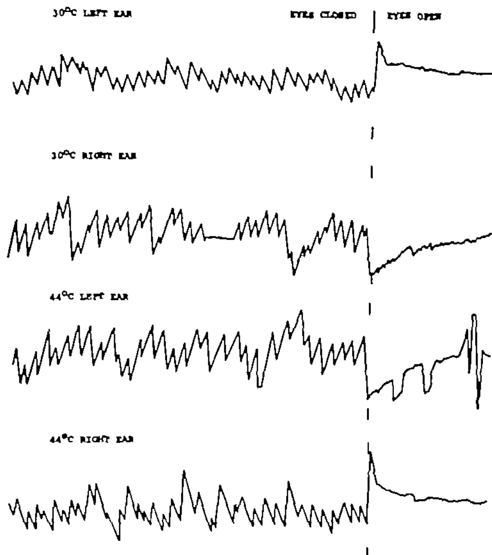


Fig 5a. An example of the normal attenuation effect engendered by opening of the eyes during the post caloric nystagmus.

(+20 diopter) convex lenses or by closing the eyes.

Unidirectional nystagmus i e always beating in the same direction when seen irrespective of the position of the eye is more suggestive of a lesion of the vestibular system proper and typically is attenuated or suppressed with ocular fixation In other words, the application of Frenzel s glasses or closing the eyes will render the nystagmus more intense It is only this latter nystagmus, recorded with the eyes closed, which is noted in this ENG analysis.

The actual recording was made with the patient seated erect with the head in the anatomical position and was made prior to the positional and caloric tests, which might induce some provoked nystagmus. A provoked spontaneous nystagmus is one that is present in the erect position not present at the beginning of the test sequence but which appears during the course of the ENG examination and persists after the normal physiologic duration of any antecedent vestibular stimulus effect has passed From a clinical point of view it has much the same significance as a spontaneous nystagmus, but of lesser degree

C Positional nystagmus

The third major portion of the electronystagmographic evaluation consisted of positional tests. Just as spontaneous nystagmus may be present only with the eyes open or with the eyes closed, so may positional nystagmus appear under varying conditions. Nystagmus may be "direction changing" beating in different direc

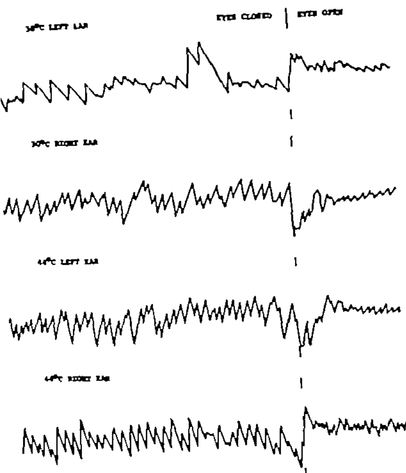


Fig 5b An example of abnormal (unnatural) attenuation effect on opening of the eyes during the post-caloric nystagmus.

tions with different positions of the head or it may be "direction fixed" always beating in the same direction whenever it is elicited. The clinical implications of unidirectionality or multidirectionality are generally the same as for spontaneous nystagmus

Again, in the ENG analysis, recordings were made only with the eyes closed Although many positions are possible, the positions tested were with the patients supine, supine with the head rotated to the left, and supine with the head rotated to the right Each position was maintained for 1 minute

D **Response to caloric stimulation**

The final tests in the vestibular work-up were the caloric tests A modification of the Hallpike technique (Fitzgerald and Hallpike, 1942) was employed according to the recommendations of the ENG study group (Rubin, 1968)

The patient rests comfortably on an examination table, flexed at the hips such that the body and head are elevated 30 from the horizontal. Thus, there is no extension or flexion of the neck relative to the main axis of the trunk. The first 75 seconds of the caloric test sequence (30 and 44 irrigations of each ear canal) are recorded with the eyes closed, whereupon the patient is requested to open his eyes and fixate on a small light in the ceiling (Hart, 1967) Recording is continued in this modality until no more visible nystagmus can be seen by direct examination of the eyes. At this point, the patient is requested to close his eyes and the nystagmus is further

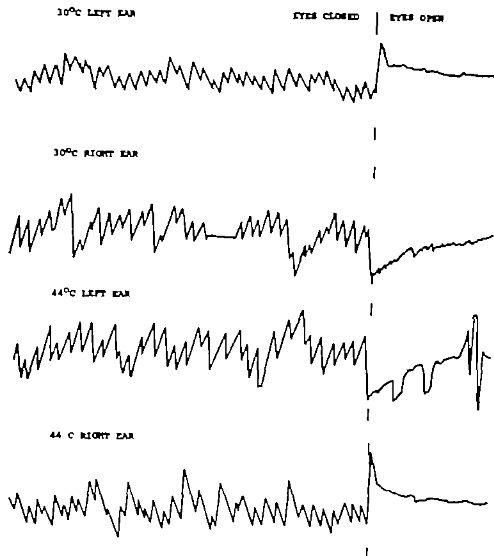


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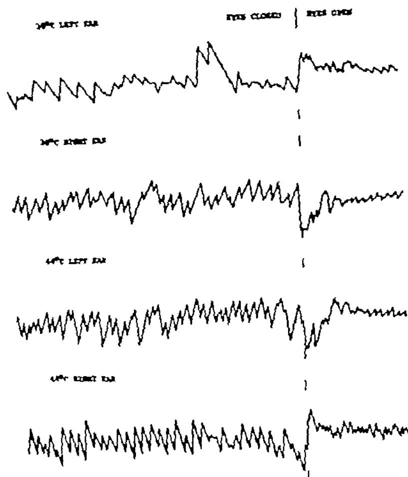


Fig. 5b. An example of abnormal (minimal) attenuation effect on opening of the eyes during the post-caloric nystagmus.

tions with different positions of the head, or it may be "direction fixed" always beating in the same direction whenever it is elicited. The clinical implications of unidirectionality or multidirectionality are generally the same as for spontaneous nystagmus.

Again, in the ENG analysis, recordings were made only with the eyes closed. Although many positions are possible, the positions tested were with the patients supine, supine with the head rotated to the left, and supine with the head rotated to the right. Each position was maintained for 1 minute.

D. Response to caloric stimulation

The final tests in the vestibular work up were the caloric tests. A modification of the Hallpike technique (Fitzgerald and Hallpike, 1942) was employed, according to the recommendations of the ENG study group (Rubin, 1968).

The patient rests comfortably on an examination table, flexed at the hips such that the body and head are elevated 30° from the horizontal. Thus, there is no extension or flexion of the neck relative to the main axis of the trunk. The first 75 seconds of the caloric test sequence (30° and 44° irrigations of each ear canal) are recorded with the eyes closed, whereupon the patient is requested to open his eyes and fixate on a small light in the ceiling (Hart, 1967). Recording is continued in this modality until no more visible nystagmus can be seen by direct examination of the eyes. At this point, the patient is requested to close his eyes and the nystagmus is further



Fig 6 An example of dysrhythmic eye movements.

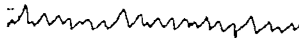


Fig 7 An example of the abnormal nystagmic be known as triangular waves.

recorded until there is no more nystagmus in the expected direction (as seen on the ENG)

Although DeManez (1968) has recommended an index of ocular fixation for this modification it was found difficult to apply during the present study Often the nystagmus with the eyes open was unmeasurable electronystagmographically because of its small amplitude Also not infrequently in some patients, no definite nystagmic pattern was seen with the eyes closed due to dysrhythmia or cortical suppression Therefore, somewhat arbitrarily when the recordings were capable of valid interpretation a reduction in the amplitude or slow phase velocity of less than 50% of the original level on opening the eyes, was considered abnormal Examples of normal and abnormal attenuation are shown in Figs 5a and b In the analysis of the maximum slow phase velocity with the eyes closed the Jongkees formula (Jongkees 1964) was applied with upper limits of normality being 15% for left right difference and 19% for directional preponderance For the duration with eyes open normal limits of 30 sec and 40 sec as recommended by Fitzgerald & Hallpike (1942) were accepted for left right difference and directional preponderance respectively

Hyperexcitability as evaluated by the maximum slow phase velocity eyes closed was said to be present if any 2 of the 4 caloric responses averaged more than 30 per second slow phase velocity This phenomenon was designated as marked if any 2 responses averaged more than 50 per second Hyperexcitability as evaluated by duration eyes open was said to be present if any 2 responses averaged more than 3 min each.

Bilateral paresis was said to be present if the sum of the 4 maximum slow phase velocities was less than 40 /second

The diagnosis of dysrhythmia was made entirely on the basis of subjective clinical judgment as no reliable means of quantifying this phenomenon have been found Henriksson (personal communication) has suggested the integration of the time differences between successive nystagmic beats as a valid measure However the equipment to do this was not available An example of dysrhythmia is shown in Fig. 6

The records were also examined for the presence of triangular waves, which in essence, represent a slowing of the fast phase. Such waves might be considered to reflect a partial lesion of the center generating the fast phase of nystagmus Although there is some difference of opinion as to where the center may be many investigators feel that it is probably in the brainstem rostral to the vestibular nuclei Triangular waves are shown in Fig 7

Thus it may be seen that the ENG examination encompasses an evaluation not only of the peripheral labyrinth but also the brain stem area cerebellum, vestibular ocular pathways and certain aspects of the visual oculo-motor system Multiple sclerosis does not affect the peripheral labyrinth, but does affect the latter areas with a high degree of frequency Therefore the ENG examination is well suited for the evaluation of the lesions of these various interconnecting systems.

VI SUMMARY

The foregoing sections have described in some detail the neurological auditory and vestibular examinations administered to a large group of persons with multiple sclerosis Sixty-one patients were given the neurological and auditory evaluations The neurological examination followed the format described in a previous study

y Rose et al. (1970). The battery of auditory ests consisted of routine audiometric techniques nd a group of special tonal and speech tests ncluding some not previously employed with clinical populations. In addition, vestibular function for 44 of the 61 multiple sclerosis patients was examined utilizing electronystagmographic techniques.



Fig 6 An example of dysrhythmic eye movements.

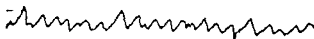


Fig 7 An example of the abnormal nystagmic beat known as triangular waves.

recorded until there is no more nystagmus in the expected direction (as seen on the ENG)

Although DeManez (1968) has recommended an index of ocular fixation for this modification it was found difficult to apply during the present study Often the nystagmus with the eyes open was unmeasurable electronystagmographically because of its small amplitude Also not infrequently in some patients, no definite nystagmic pattern was seen with the eyes closed due to dysrhythmia or cortical suppression Therefore somewhat arbitrarily when the recordings were capable of valid interpretation a reduction in the amplitude or slow phase velocity of less than 50 % of the original level on opening the eyes, was considered abnormal Examples of normal and abnormal attenuation are shown in Figs 5a and b In the analysis of the maximum slow phase velocity with the eyes closed the Jongkees formula (Jongkees 1964) was applied, with upper limits of normality being 15 % for left right difference and 19 % for directional preponderance. For the duration with eyes open, normal limits of 30 sec and 40 sec as recommended by Fitzgerald & Hallpike (1942) were accepted for left right difference and directional preponderance, respectively

Hyperexcitability as evaluated by the maximum slow phase velocity eyes closed was said to be present if any 2 of the 4 caloric responses averaged more than 30 per second slow phase velocity This phenomenon was designated as "marked if any 2 responses averaged more than 50° per second Hyperexcitability as evaluated by duration eyes open was said to be present if any 2 responses averaged more than 3 min each.

Bilateral paresis was said to be present if the sum of the 4 maximum slow phase velocities was less than 40 /second.

The diagnosis of dysrhythmia was made entirely on the basis of subjective clinical judgment as no reliable means of quantifying this phenomenon have been found Henriksson (personal communication) has suggested the integration of the time differences between successive nystagmic beats as a valid measure However the equipment to do this was not available An example of dysrhythmia is shown in Fig. 6.

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VI SUMMARY

The foregoing sections have described in some detail the neurological auditory and vestibular examinations administered to a large group of persons with multiple sclerosis Sixty-one patients were given the neurological and auditory evaluations. The neurological examination followed the format described in a previous study

Table I *Incidence (percentage) of selected neurological signs and symptoms for 61 patients with multiple sclerosis*

Signs and Symptomatology	
Spasticity and hyperreflexia	98
Sphincter disturbance and/or impotence	95
Difficulty with coordination, gait, and/or upper extremities	90
Weakness	85
Paresthesias	60
Medial longitudinal fasciculus syndrome	54
Optic atrophy	50
Diplopia and oscillopsia	50
Gamma globulin elevation	46
Cranial nerve	30
Auditory	7

can group the subjects according to general site of lesion and extent of damage and then consider the auditory test data in light of these groupings. This is done later in the paper

II AUDIOLOGICAL FINDINGS

An abstract of the auditory tests administered to the 61 multiple sclerotics is given for each ear in Table III In the cases of the tone decay Békésy SISI ABLB, and SBMPL tests, the most noteworthy finding among those from the several frequencies tested is reported in the table. The findings that emerged are summarized below first for each test separately and then for rela-

Table II *Incidence (number of persons) of sites of lesion for 61 patients with multiple sclerosis inferred from neurological evaluation*

Level of lesion labelled as in Fig 8 Incidence of spinal cord involvement shown separately

Level	Number	Spinal cord incidence[a]
No neural signs	1	
1 (only)	1	
2 (only)	1	1
3 (only)		
4 (only)	8	7
1 and 3	1	1
1 and 4	8	3
2 and 4		1
3 and 4	2	2
1 2, and 3	9	6
1 2, and 4	2	1
1 3 and 4	1	1
2, 3, and 4	10	8
1 2, 3, and 4	8	3

[a] Seven persons presented with only spinal cord signs

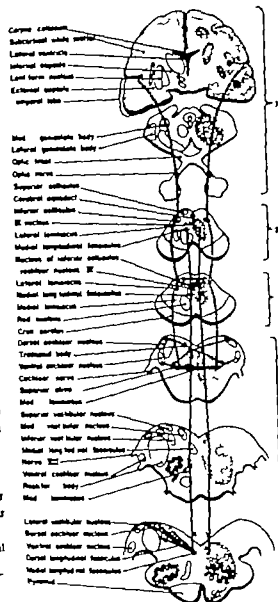


Fig 8 Serial transverse sections of human brain at various levels, featuring major auditory and vestibular tracts and other highlights of the central nervous system (Level 1 cortico-optic, Levels 2 and 3 midbrain, and Level 4 brainstem) Shaded areas indicate the approximate location of common anatomical sites of sclerotic lesion. Although clinical observations suggested involvement could be multileveled and unilateral or bilateral, only half of each section is shaded for the sake of clarity

3 Results

I NEUROLOGICAL FINDINGS

The neurological findings for the 61 subjects under study are given in Table I This table reports the incidence of certain neurological signs and symptoms encountered in this group of multiple sclerotic patients The amount of overlap in the indicated percentages reveals the multiple involvement of the disease process throughout the central nervous system of these patients From this table, it is apparent that assorted motor and cerebellar disturbances were most common in this group In addition medial longitudinal fasciculus (MLF) syndrome was evident in 54 % of the subjects paresthesias (60 %), diplopia and oscillopsia (50 %) optic atrophy (50 %), and gamma globulin elevation (46) were similarly prevalent. Auditory complaints as presenting symptoms were rare 7 %

The above stated figures are quite similar to earlier reports of incidences of findings in multiple sclerosis (e g. Carter et al 1950 Poser 1966) Thus this population appears to be typical

Table II details the neuroanatomical involvements which were judged by the neurologist to have been present in these patients Here the population is divided according to the inferred sites of lesions. This table should be studied in conjunction with Fig. 8 which was developed to assist in clarifying suspected sites of lesion The figure gives a schematic representation of the auditory and vestibular tracts. Notice in the figure that the central nervous system has been divided into 4 major levels representing the cortical and optic zone (level 1) the midbrain (2 and 3) and the brainstem (4) Within this schematic the major auditory and vestibular crossings and nuclei are labelled The right half of each section also contains stippled regions corresponding to sites of predilection for sclerotic foci It should be mentioned that the lesions may be extensive and *bilateral* The "level" column in Table II reports which of the levels shown in Fig. 8 were inferred to have been involved in the 61 patients. A separate column gives the number of cases who also had symptoms referred to spinal cord lesions. Notice that the neurological evaluations suggested that all but 8 of the 61 subjects had symptoms referrable to lesions at 1 or more of the levels depicted in Fig. 8 One of these 8 had no neurological symptoms at examination and the other 7 revealed symptomatology attributable to spinal cord damage. However it is of interest that all 7 patients with only spinal cord symptoms at neurological evaluation yielded at least 1 noteworthy auditory finding.

One area of considerable interest is Level 4 wherein lies the central portions of the VIIIth cranial nerve the auditory and vestibular nuclei, and the trapezoid bodies. A total of 67 of the 61 subjects had symptoms thought due to lesions at this level of the CNS However 76 of the group with Level 4 lesions gave primarily cerebellar signs, 10 % had symptoms of purely low brainstem (non-cerebellar) lesions and 14 had signs of both cerebellar and non-cerebellar Level 4 lesions. Lesions in the midbrain were inferred to be present in a considerable number of the subjects 51 were thought to have lesions in Level 3 52 in Level 2 Lesions thought present at the cortico-optic level were slightly less prevalent, 50 %. Symptoms attributable to spinal cord damage were observed in 67 of the subjects and 12 of the 61 subjects had only spinal cord signs at the time of the neurological examination

Not surprisingly many subjects gave evidence of wide-spread lesions in the CNS However one

onal tests

Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	MLD 500 Hz (dB)	MLD speech (dB)	Vestibular abnormalities	Inferred sites of lesion
110	IV	N	ED	EE			A, B C, F J	1 2, 3 5
0	I	N	—					
70	IV	I	UR	UE				2, 3, 4, 5
15	II		—					
55	II	D	UR	UE				1, 2, 3 5
45	II	N	—					
Would not tolerate further threshold or suprathreshold testing, signals just above threshold were painful								1 2, 3, 5
35	II	D	EE	EE				1 2, 3
25	II	N						
10	I	D	EE	EE				1 4 5
10	II	D						
30	II	D	EE	EF	2		A, B, E, G, H K	1 2, 3
45	II	D						
40	IV	D	—	EE				2, 3, 4
100	IV	D	ED					
20	II	N	UN	UE	11		A, B C, D F G	4, 5
5	I	N	—					
15	II	N	EE	EE	8	5	D F H	4, 5
10	II	N						
5	II	N	—	UE	11		C, D I	1 4
25	II	I	UR					
5	II	N	—	EE	10	3	A, B D F G H, J	1 2, 3 4
5	I	N	ED					
40	II	N	EE	EE	10			
10	II	D						1
45	III	D	ED	EU	−1	−1	A, B, G	2, 3 4, 5
60	III	D	—					
60	II	D	ED	EE	8			
40	IV	D	—					2, 4, 5
5	I	N	—	EE	5	−3	B, C, D I J	
10	II	N	ED					1 4
35	II	D	EE	EE				
0	II	N						1 2, 3 4

Table III *Results of auditory vestibular and neurological evaluation for 61 patients with multiple sclerosis*
See end of table for keys to codings used

					Speech tests[b]					
Subj no.	Age	Sex	Ear	*Pure tone configuration*, severity of loss[a]	500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination ( )	Competing speech ( )	Speech in white noise ( )	Filtered speech (N–A)
1	47	M	R	Arched normal	5	10	94		44	
			L	Arched low normal, high moderate	5	0	100		78	
[illegible]	53	M	R	Arched low mild high severe	7	–	94			N
			L	Arched, low mild, high mild	1	4	98			N
3	28	F	R	Arched low mild, high severe	30	28	100			
			L	Arched normal	7	6	98			
4	46		R	gradually falling low moderate, high severe	47	32	94			
			L	Flat severe	90	CNT	CNT			
5	46	M	R	Flat normal	3	−2	100	96	9	N
			L	Flat, normal		−6	100	9	88	A
6	[illegible]5	F	R	Flat, normal	12	4	96	96	62	N
			L	Arched low normal, high mild	13	3	100	9	76	N
7	37	M	R	Notched –6 KHz; severe	[illegible]0	10	86	72	44	A
			L	Notched –6 KHz severe	[illegible]2	10	70	60	36	A
8	[illegible]1	M	R	Flat normal	[illegible]0	[illegible]2	90		36	
			L	Flat normal	18	[illegible]0	66		14	
9	52	F	R	Arched low mild high moderate	3	24	96	100	60	N
			L	High frequency loss, mild	12	6	100	96	66	N
10	33	M	R	Flat normal	10	1	100	100	82	N
			L	Rising mild	18	5	100	100	8[illegible]	N
11	34	F	R	Flat mild	7	19	100	100	74	N
			L	Notched 4–6 KHz; moderate	28	21	100	100	68	N
12	49	F	R	Flat, normal	10	7	96	96	70	N
			L	Notched 1 KHz, normal	12	4	100	100	62	A
13	27	F	R	Flat normal	5	6	96	96	6[illegible]	N
			L	Flat normal	3	6	96	86	48	A
14	36	F	R	Arched low mild, high mild	20	19	100	100	64	N
			L	Arched low mild, high mild	20	11	100	96	44	N
15	5[illegible]	F	R	Flat normal	17	12	96	100	46	
			L	Flat normal	13	14	100	96	50	
16	23	F	R	Flat normal	5	−1	100	100	80	
			L	Rising normal	7	−4	100	9	66	
17	53	M	R	Flat normal	8	9	100	96	54	N
			L	high frequency loss, mild	7	11	96	100	64	N

Tonal tests								
Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	MLD 500 Hz (dB)	MLD speech (dB)	Vestibular abnormalities[e]	Inferred sites of lesion[f]
110 [d]	IV	N	ED	EE			A, B, C, F J	1 2, 3 5
0	I	N	—					
70	IV	I	UR	UE				2, 3 4, 5
15	II		—					
35	II	D	UR	UE				1 2, 3, 5
45	II	N	—					
Would not tolerate further threshold or suprathreshold testing; signals just above threshold were painful								1 2, 3 5
15	II	D	EE	EE				1 2, 3
25	II	N						
10	I	D	EE	EE				1 4, 5
10	II	D						
30	II	D	EE	EF	2		A, B, E, G H K	1 2 3
45	II	D						
90	IV	D	—	EE				
100	IV	D	ED					2, 3 4
20	II	N	UN	UE	11		A, B, C, D F G	4, 5
5	I	N	—					
15	II	N	EE	EE	8	5	D F H	4, 5
10	II	N						
5	II	N	—	UE	11		C, D I	1 4
25	II	I	UR					
5	II	N	—	EE	10	3	A, B, D F G H, J	1 ~, 3, 4
5	I	N	ED					
40	II	N	EE	EE	10			
10	II	D						1
45	III	D	ED	EU	−1	−1	A, B, G	2, 3, 4 5
60	III	D	—					
60	II	D	ED	EE	8			
60	IV	D	—					2, 4, 5
3	I	N	—	EE	5	−3	B, C, D I J	1 4
10	II	N	ED					
35	II	D	EE	EE				
0	II	N						1 2, 3, 4

Table III (Cont)

Subj no	Age	Sex	Ear	Pure tone configuration, severity of loss[a]	Speech tests[b] 500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination (%)	Competing speech (%)	Speech in white noise ( )	Filtered speech (N A)
18	35	M	R	Flat normal	17	18	96	98	70	N
			L	Arched normal	13	15	94	92	70	N
19	36	M	R	Flat mild	27	23	100	100	84	N
			L	Notched 1–4 KHz; mild	28	23	100	90	68	A
20	49	F	R	Arched low normal high mild	8	5	100	100	74	N
			L	Arched normal	10	3	100	100	70	N
1	51	F	R	Arched normal	2	6	96	96	70	N
			L	Arched, normal	3	4	92	92	64	N
22	64	F	R	Notched 6 KHz; moderate	20	12	96		64	
			L	Gradually falling, severe	57	63	4			
23	46	F	R	Flat normal	13	1	96	100	6[illegible]	
			L	Flat normal	10	1	96	100	80	
24	27	M	R	Arched normal	8	6	100	100	76	N
			L	Flat normal	5	4	100	100	82	N
25	48	M	R	Arched low moderate, high severe	30	30	88	72	3	
			L	Arched low moderate, high severe	3	31	86	68	4	
26	46	M	R	Notched 1 KHz + 3–6 KHz moderate	22	23	96	9	50	N
			L	Notched 1K + 4 KHz; *mild*	22	20	96	100	50	N
27	44	M	R	Arched low mild, high moderate	5	6	96	96	60	
			L	Arched low mild, high moderate	12	5	96	9	74	
28	59	F	R	Rising; mild	15	14	100	80	46	N
			L	Rising, normal	15	1	96	20	42	A
29	55	F	R	Flat, normal	5	0	98	100	7[illegible]	
			L	Flat, normal	5	3	100	96	66	
30	37	F	R	Rising; normal	3	6	96	96	8[illegible]	N
			L	Rising, normal	3	8	100	92	68	N
31	45	M	R	High frequency loss moderate	12		50	0	4	
			L	High frequency loss *mild*	5	2	100	96	54	
32	62	M	R	Arched low mild, high moderate	17	11	92	58	48	
			L	High frequency loss mild	13	4	100	9[illegible]	7[illegible]	
33	26	F	R	Rising; mild	20	17	96	9[illegible]	74	N
			L	Rising normal	15	14	96	96	72	N
34	33	F	R	Arched low moderate, high severe (conducti e)	53	59	96		7[illegible]	
			L	Arched normal	18	9	100		76	

Tonal tests					MLD			
Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	500 Hz (dB)	speech (dB)	Vestibular abnormalities[e]	Inferred sites of lesion[f]
5	II	N	EE	EE	9	6	F	None
5	II	N						
10	I	I	EE	EE	6	4	A, B C, D E, F G	1 2, 3 4 5
25	I	I						
50	II	I	EE	EE	8			4, 5
55	II	I						
25	I	N	EE	EE	7	9	C, I	5
10	II	D						
5	II	I	—	UE	4	3	C, D E, F H, I, J	4 5
10	II	I	UR					
60	IV	D	EE	EF	0	1	D, E, G H, I	1 2, 3, 4, 5
55	IV	D						
15	I	D	EE	EU	5	4	A, E, H, I	1 4 5
15	II	D						
10	II	D	EE	EU	0	3	B, G J	1 2, 3 4
25	II	D						
30	II	I	UR	UE	7	6		4
20	II	N	—					
20	II	N	ED	EE	5	5		5
15	II	D	—					
30	IV	D	EE	EE	14	5	A, C, D, I	5
45	II	D						
5	II	D	EE	EE	15	6		5
10	I	D						
0	II	N	EE	EE	10	5		1 4
5	I	D						
90	IV	D	ED	EE	4	0	B, C, D F J	2, 3, 4 5
10	II	I	—					
40	CNT[g]	D	UN	UE	CNT[g]			
35	CNT[g]	D	—					1 2, 3, 4
25	II		EE	EE	4	4		
15	I							
10		D	UN	UU	−2			1 2, 3 5
5	II	N	—					2, 3 4 5

Table III (Cont.)

Subj no	Age	Sex	Ear	Pure tone configuration severity of loss[a]	Speech tests[b] 500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination (%)	Competing speech (%)	Speech in white noise (%)	Filtered speech (N-A)
18	35	M	R	Flat normal	17	18	96	98	70	N
			L	Arched normal	13	15	94	92	70	N
19	36	M	R	Flat mild	27	23	100	100	84	N
			L	Notched 1–4 KHz; mild	28	23	100	90	68	A
20	49	F	R	Arched low normal high mild	8	5	100	100	74	N
			L	Arched normal	10	3	100	100	70	N
21	51	F	R	Arched normal	2	6	96	96	70	N
			L	Arched normal	3	4	92	92	64	N
22	64	F	R	Notched 6 KHz; moderate	20	12	96		64	
			L	*Gradually falling severe*	57	63	4			
23	46	F	R	Flat normal	13	1	96	100	62	
			L	Flat normal	10	1	96	100	80	
24	7	M	R	Arched normal	8	6	100	100	76	N
			L	Flat normal	5	4	100	100	8[illegible]	N
25	48	M	R	Arched low moderate, high severe	30	30	88	72	32	
			L	Arched low moderate, high severe	32	31	86	68	4	
26	46	M	R	Notched 1 KHz + 3–6 KHz; moderate	22	23	96	92	50	N
			L	Notched 1K + 4 KHz, mild	22	20	96	100	50	N
27	44	M	R	*Arched low mild,* high moderate	5	6	96	96	60	
			L	Arched low mild, high moderate	12	5	96	9	74	
28	59	F	R	Rising mild	15	14	100	80	46	N
			L	Rising, normal	15	1	96	20	4	A
29	55	F	R	Flat normal	5	0	98	100	72	
			L	Flat normal	5	3	100	96	66	
30	37	F	R	Rising; normal	3	6	96	96	82	N
			L	Rising; normal	3	8	100	92	68	N
31	45	M	R	High frequency loss moderate	12	2	50	0	4	
			L	*High frequency loss* mild	5		100	96	54	
32	62	M	R	Arched low mild, high moderate	17	11	92	58	48	
			L	*High frequency loss,* mild	13	4	100	92	7[illegible]	
33	46	F	R	Rising, mild	20	17	96	92	74	N
			L	Rising; normal	15	14	96	96	72	N
34	33	F	R	Arched low moderate, high severe (conductive)	53	59	96		7[illegible]	
			L	Arched normal	18	9	100		76	

Ear #	Tonal tests[f] Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	MLD 500 Hz (dB)	MLD speech (dB)	Vestibular abnormalities[f]	Inferred sites of lesion[f]
	5	II	N	EE	EE	0	1	A, B, D E, H	4 5
	5	I	N						
	30	I	N	EE	EE	6	3	F J	2, 3 4
	30	I	N						
	0	I	D	EE	EE	11	7	A, B, D E, G H K	1 2, 4 5
	0	I	D						
	10	I	D	EE	EF	8	4	A, B, C, D E, G H I	3 4 5
	10	I	D						
	45	IV	D	CNT	UE	0	2	A B, E, G	1 4, 5
	40	IV	D						
	5	I	N	EE	EE	13	12	A, B C G H, I	1 4
	15	I	D						
	50	I	N	EE	EE	13	4	B, D E, H, J	2, 4
	60	I	N						
	45	II	N	EE	EE	10	3	B, C, D F I	2, 5
	40	II	N						
	25	II	D	EE	EE	15	9	C, D E, H	5
	20	II	D						
	10	CNT[g]	N	EE	EE	CNT[g]	5	—	4, 5
	5	CNT[g]	N						
	25	II	N	EE	EE	10	8	A, B, C, D, J	5
	50	IV	N						
	45	IV	D	EE	EE	0	3	A, B, C, E, G, H, I	1 2, 3, 5
	40	IV	D						
	10	II	I	—	UE	0	1	A, E, F G I	1 2, 3, 4 5
	35	II	I	UR					
	10	II	N	—	UE	10	7	C	1 2, 3
	5	II	N	UR					
	0	I	N	UR	UU	6	4	C, I	5
	0	I	N	—					
	30	IV	D	ED	EE	7	2	A, B, F G J	1 3, 4
	25	II	D	—					
	50	IV	D	EE	EU		4	A, D, G	1 3, 4, 5
	40	IV	D						
	15	I	N	EE	EE	9	5	A, C, D E, F H I	1 3 5
	20	I	N						
	15	II	N	EE	EE	10	8	A, B, E, J K	1 4
	10	II	N						

Table III (Cont.)

Subj no	Age	Sex	Ear	*Pure tone configuration* severity of loss[a]	Speech tests[b]: 500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination ( )	Competing speech ( )	Speech in white noise ( )	Filtered speech (N-A)
35	42	M	R	Flat normal	5	5	96	9[illegible]	64	N
			L	Notched 6 KHz, normal	[illegible]	7	96	100	7[illegible]	N
36	27	M	R	Flat, normal	10	8	96	96	68	
			L	Notched 1 KHz, normal	10	8	92	9[illegible]	70	
37	21	F	R	Rising; normal	3	0	96	96	84	N
			L	Flat normal	−2	0	96	96	80	N
38	57	M	R	Gradually falling, severe	33	22	96	92	80	
			L	Gradually falling; severe	3	[illegible]1	96	96	78	
39	42	F	R	Flat normal	7	1	100	9[illegible]	78	N
			L	Notched 1 KHz, normal	17	7	92	78	64	A
40	3[illegible]	M	R	Rising but notched 4–6 KHz; mild	17	9	100	9[illegible]	70	N
			L	Flat normal	15	9	100	92	80	N
41	51	F	R	Notched 4 KHz, mild	8	4	100	96	80	
			L	High frequency loss, mild	6	6	100	96	84	
42	32	F	R	*Gradually falling: mild*	*8*	*2*	*92*	*92*	*76*	
			L	Gradually falling; mild	5	2	96	96	74	
43	62	F	R	Gradually falling: moderate	25	17	92	96	60	
			L	Gradually falling moderate	17	10	92	92	58	
44	5[illegible]	F	R	Mid-frequency loss mild	[illegible]5	14	100	100	58	N
			L	Mid-frequency loss, mild	23	18	100	100	64	N
45	39	F	R	Flat normal	0	1	9[illegible]	9[illegible]	7[illegible]	N
			L	Flat normal	6	−1	96	92	7[illegible]	N
46	36	M	R	High frequency loss but notched 1 KHz, mild	25	19	96	88	6[illegible]	N
			L	High frequency loss mild	18	12	92	90	70	N
47	43	M	R	Mid-frequency loss mild	25	20	100	100	66	
			L	Sharply falling; moderate	28	24	84	76	50	
48	50	M	R	Notched 6 KHz mild	8	8	96	96	86	N
			L	Notched 4–6 KHz, mild	*12*	*10*	96	96	82	N
49	43	M	R	Arched low normal, high mild	22	18	100	96	7[illegible]	N
		M	L	Flat normal	0	3	100	100	88	N
50	53	F	R	Flat normal	1	11	94	96	64	N
			L	Arched normal	3	7	80	74	46	N
51	41	F	R	Gradually falling, mild	15	18	96	9[illegible]	58	N
			L	Gradually falling: mild	18	16	96	88	56	N
52	38	M	R	Arched normal	10	5	100	9[illegible]	80	
			L	Arched low normal high mild	8	5	100	90	88	
53	37	M	R	Flat, normal	13	−2	100	90	80	
			L	Flat normal	13	0	100	9[illegible]	8[illegible]	

Tonal tests[f]					MLD			
Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	500 Hz (dB)	speech (dB)	Vestibular abnormalities[e]	Inferred sites of lesion[f]
5 5	II I	N N	EE	EE	0	1	A, B, D E, H	4, 5
30 10	I I	N N	EE	EE	6	3	F J	2, 3 4
0 0	I I	D D	EE	EE	11	7	A, B, D E, G H, K	1 2, 4, 5
10 10	I I	D D	EE	EF	8	4	A, B, C, D E, G H, I	3, 4 5
45 40	IV IV	D D	CNT	UE	0		A B, E, G	1 4 5
5	I	N	EE	EF	13	12	A, B, C, G, H, I	1 4
15	I	D						
30 60	I I	N N	EE	EE	13	4	B, D E, H, J	–, 4
45 60	II II	N N	EE	EE	10	3	B C, D F I	2, 5
25	II	D	EE	EE	15	9	C, D E, H	5
20	II	D						
10	CNT[g]	N	EE	EE	CNT[g]	5	—	4, 5
5	CNT[g]	N						
25 30	II IV	N N	EE	EE	10	8	A, B, C, D J	5
45	IV	D	EE	EE	0	3	A, B, C, E, G H I	1 2, 3 5
40	IV	D						
10	II	I	—	UE	0	1	A, E, F G, I	1 2, 3 4 5
35	II	I	UR					
10 5	II II	N N	— UR	UE	10	7	C	1 –, 3
0	I	N	UR	UU	6	4	C, I	5
0	I	N	—					
30 25	IV II	D D	ED —	EE	7	2	A, B, F G J	1 2 3, 4
40 50	IV IV	D D	EE	EU		4	A, D G	1 3, 4, 5
15 20	I I	N N	EE	EE	9	5	A, C, D, E, F H, I	1 3 5
15 10	II II	N N	EE	EE	10	8	A, B, E, J K	1 4

Table III (Cont)

Subj. no	Age	Sex	Ear	Pure tone configuration, severity of loss[a]	Speech tests[b]					
					500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination (%)	Competing speech (%)	Speech in white noise (%)	Filtered speech (N–A)
54	47	F	R	Low frequency loss, mild	20	9	100	96	90	
			L	Rising; normal	13	5	96	90	90	
55	59	F	R	Gradually falling; moderate	18	19	100	100	52	
			L	Gradually falling; mild	17	12	100	82	56	
56	20	F	R	Arched normal	8	6	96	100	74	N
			L	Rising normal	8	3	96	100	80	N
57	25	F	R	Flat, normal	7	4	100	96	74	N
			L	Flat normal	7	4	100	98	66	N
58	28	F	R	Rising; mild	20	21	96	90	68	A
			L	Rising mild	25	23	100	94	84	N
59	37	F	R	High frequency loss, mild	5	1	100	92	70	N
			L	Notched 6 kHz; mild	0	−3	96	92	68	N
60	38	M	R	Flat, normal	13	10	100	92	70	
			L	Flat normal	13	10	100	92	58	
61	20	F	R	Flat normal	3	4	100	100	80	N
			L	Flat normal	3	1	100	100	74	N

tionships between tests Vestibular abnormalities and sites of lesion inferred from the neurological examinations are also presented in Table III

A Results for individual tests

1 *Pure tone thresholds and configurations*

The thresholds at the several test frequencies are not given in Table III Instead Column 5 of the table presents 2 types of information the configuration of the audiogram and whether or not a hearing loss was present at some point(s) across the frequency range The categories for the audiometric configuration conform to general usage (Carhart, 1945) except for the arched configuration [1]

Hearing loss is here defined as a pure tone threshold exceeding 25 dB hearing level (ANSI 1969) at one or more audiometric test frequencies in the 125–8 000 Hz range There were 64 ears (of a possible 122 ears) for which such a deficiency was found Of these 64 ears, 39 ears had no threshold exceeding 35 dB (a mild loss), 13 ears had at least one threshold in the range 40–65 dB and 12 ears had one or more thresholds which exceeded 65 dB

Twenty three persons (and thus 46 of 64 ears with hearing loss) had bilateral hearing losses. Fourteen of these persons had bilaterally symmetrical threshold configurations, but only 11 of them had bilaterally symmetrical and equally

[1] The arched configuration is characterized by better sensitivity for the mid-frequencies than for either low or high frequencies. The pattern is labelled arched because threshold sensitivity drops fairly symmetrically to poorer but not necessarily equal levels at both low and high frequencies. A variant of the arched configuration is the lazy S contour a threshold pattern also marked by best hearing in the mid frequencies, but in which the poorest threshold at the low frequency end occurs at 500 Hz, i e thresholds worsen from 125–500 Hz, improve in the mid-frequencies, and worsen again at higher frequencies. (However a clear lazy-S pattern was not observed in this sample of 122 ears) These patterns have been previously associated with multiple sclerosis (Bentzen et al 1951 Preibsch-Effenberger 1963 Dayal & Swisher 1967 Kehajov 1967 Chladek, 1968).

Tonal tests[a]					MLD			
Threshold tone decay (dB)	Békésy (Type)	SISI	ABLB	SBMPL	500 Hz (dB)	speech (dB)	Vestibular abnormalities[e]	Inferred sites of lesion[f]
15	II	N	EE	EE	12	4	A, E, G, J	2, 3, 4, S
10	II	N						
55	II	I	EE	EE	1	2	B, E, F, H, J	2, 3, 4, S
45	II	I						
5	I	N	EE	EE			D, E, F, J	4, S
6	I	D						
5	I	N	EE	EF			A, E,	2, 3, 4, S
10	I	N						
20	II	D	EE	EE			A, B, D, G, H, I, J	1–4
15	I	D						
40	II	D	—	EF	13	9	H	3, 4, S
45	II	N	ED					
15	I	D	ED	EU	3	1	A, F	1, 2, 3
0	I	D	—					
10	II	N	EE	EE	10	10	A, B, D, E, H, I, J	2, 3, 4, S
10	II	N						

Mild 30–35 dB, moderate 40–65 dB, severe 65 dB.
Speech discrimination was measured at these levels unless otherwise specified: in quiet @ 40 dB SL re SRT; against contralateral speech competition @ 50 dB SL re SRT with (contralateral) competition at 60 dB SL re SRT (S/C = −10); in white noise (monaural) @ 40 dB SL re SRT (S/N 0); filtered (monaural and binaural) @ 26 dB re relevant SRTs. The filtered performance involved four scores and was graded N normal or A abnormal. For explanations of normality and abnormality and further details on all of the speech procedures, see the text.
The tonal tests and the MLD for speech were administered in the usual fashion as was discussed in the text. The results listed in the table are the most outstanding at one or more frequencies in the specified ear except the results of loudness balancing (ABLB) were assigned to an ear when possible (e.g., in cases of decruitment) but were otherwise assigned to the person; the binaural tests, median plane localization and masking level differences, were assigned to persons.
The SISI results were graded I increased, D decreased, and N normal. See the text.
The code for ABLB was assigned as follows: EE equal thresholds, equal rates of loudness growth; ED = equal thresholds, decruitment (in the designated ear); UR unequal thresholds (10 dB), recruitment; UD unequal thresholds, decruitment; UN unequal thresholds, no recruitment.
The code for SBMPL was assigned as follows: EE equal thresholds, midline at equal intensities; EU equal thresholds, midline at unequal intensities (10 dB); EF equal thresholds, failed to experience midline; UE unequal thresholds (10 dB), midline at equal intensities; UU unequal thresholds, midline at unequal intensities; UF unequal thresholds, failed to experience midline.
The MLDs represent the difference between thresholds in SoNo and Sπ No conditions. See text.
( ) in tone decay results: decay beyond equipment limits.
The code for the vestibular abnormalities (see Table VI and explanation thereof) was assigned thusly: A abnormal optokinetic tracking, B abnormal pendulum tracking, C positional nystagmus, D post-caloric hyperexcitability, E poor or reversed attenuation effect, F unilateral paresis, G abnormal slow tracking, H dysrhythmia, I spontaneous nystagmus, J directional preponderance, and K lateral gaze imbalance.
The inferred sites of lesion from the neurological evaluation correspond to Levels 1 (cortico-optic), 2 (midbrain at superior colliculus), 3 (midbrain at inferior colliculus), and 4 (brainstem at auditory and vestibular nuclei) in Fig. 8. An (S) in this column means that neurological signs of spinal cord lesion were present.
Could not operate band switch.

severe hearing losses. It is interesting that of the multiple sclerotic patients with hearing loss in this sample, more had bilateral deficits than had unilateral deficits.

Sensitivity of 25 dB HL or better at all frequencies was obtained via 58 ears. Such performance was listed as normal in Table III. Of course, it was possible for an audiogram in this

Table III (Cont.)

					Speech tests[b]					
Subj. no	Age	Sex	Ear	Pure tone configuration, severity of loss[a]	500–2 000 Hz Average (dB)	Speech reception threshold (dB)	Speech discrimination (%)	Competing speech ( )	Speech in white noise (%)	Filtered speech (N A)
54	47	F	R	Low frequency loss, mild	20	9	100	96	90	
			L	Rising normal	13	5	96	90	90	
55	59	F	R	Gradually falling moderate	18	19	100	100	5[illegible]	
			L	Gradually falling; mild	17	12	100	82	56	
56	20	F	R	Arched normal	8	6	96	100	74	N
			L	Rising normal	8	3	96	100	80	N
57	25	F	R	Flat, normal	7	4	100	96	74	N
			L	Flat normal	7	4	100	98	66	N
58	28	F	R	Rising; mild	20	21	96	90	68	A
			L	Rising mild	[illegible]5	23	100	94	84	N
59	37	F	R	High frequency loss mild	5	1	100	9	70	N
			L	Notched 6 kHz; mild	0	−3	96	9[illegible]	68	N
60	38	M	R	Flat normal	13	10	100	9[illegible]	70	
			L	Flat, normal	13	10	100	92	58	
61	20	F	R	Flat normal	3	4	100	100	80	N
			L	Flat, normal	3	1	100	100	74	N

tionships between tests. Vestibular abnormalities and sites of lesion inferred from the neurological examinations are also presented in Table III

A. Results for individual tests

1 *Pure tone thresholds and configurations*

The thresholds at the several test frequencies are not given in Table III Instead Column 5 of the table presents 2 types of information the configuration of the audiogram and whether or not a hearing loss was present at some point(s) across the frequency range The categories for the audiometric configuration conform to general usage (Carhart 1945) except for the arched configuration.[1]

Hearing loss is here defined as a pure tone threshold exceeding 25 dB hearing level (ANSI 1969) at one or more audiometric test frequencies in the 125–8 000 Hz range There were 64 ears (of a possible 122 ears) for which such a deficiency was found Of these 64 ears, 39 ears had no threshold exceeding 35 dB (a mild loss), 13 ears had at least one threshold in the range 40–65 dB and 12 ears had one or more thresholds which exceeded 65 dB

Twenty three persons (and thus 46 of 64 ears with hearing loss) had bilateral hearing losses. Fourteen of these persons had bilaterally symmetrical threshold configurations, but only 11 of them had bilaterally symmetrical and equally

[1] The arched configuration is characterized by better sensitivity for the mid-frequencies than for either low or high frequencies. The pattern is labelled arched because threshold sensitivity drops fairly symmetrically to poorer but not necessarily equal levels at both low nd high frequencies. A variant of the arched configuration is the lazy-S contour a threshold pattern also marked by best hearing in the mid-frequencies, but in which the poorest threshold at the low frequency end occurs at 500 Hz, i e thresholds worsen from 125–500 Hz, improve in the mid frequencies, and worsen again at higher frequencies (However a clear lazy-S pattern was not observed in this sample of 122 ears.) These patterns ha e been previously associated with multiple sclerosis (Bentzen et al 1951 Preibsh-Effenberger 1963 Dayal & Swischer 1967 Kehajov 1967 Chladek 1968).

reduced correct discrimination by more than 10 %. Of the 8 ears with normal speech discrimination in quiet, but reduced discrimination in the competing message condition, 5 of 8 exhibited decreased performance exceeding 10 %. In 3 instances, the scores were dramatically reduced (34–76 %), and in 2 of these cases, the scores in quiet were normal.

Discrimination for monosyllables when white noise was present in the same ear was obtained from 115 ears. This procedure was administered with a S/N ratio of 0 dB at a presentation level of 40 dB re the relevant SRT. Normal hearers in similar circumstances obtain scores of 70–80 % correct. In contrast, scores below 60 % were attained 28 times in this sample of multiple sclerosis subjects. In addition, 9 persons of the 57 tested had an interaural disparity in correct response rate exceeding 10 % on this test, even though the scores for both ears were 60 % or better.

The filtered speech test was administered to 36 persons (72 ears). This test, it will be recalled, involved simultaneous presentation of 2 passbands (a low frequency band and a high frequency band) of lists of 50 monosyllabic words to the listener in 4 ways: both bands to the right ear, both bands to the left ear, low band pass to the left ear with high band pass to the right ear and vice versa. Results were interpreted separately for each ear of stimulus entry. Since normal hearers correctly identify about 80 % of the filtered monosyllables regardless of whether the task was a monaural one or a binaural one, scores below 60 % in any situation or differences between ears exceeding 10 % in monaural situations were considered abnormal. Eight of 36 persons who took the test showed abnormal behavior on it: 1 via both ears and the other 7 monaurally. The subject with binaurally aberrant behavior scored less than 60 % for all test conditions. The scores for the other 7 persons were all greater than 60 %, but the interaural difference exceeded 10 %.

4. *Threshold tone decay*

The Carhart threshold tone decay test was administered at 1 or more frequencies to 120 ears. Results are reported in Table III. In 82 instances, the amount of adaptation which was measured ranged between 0 and 30 dB at all frequencies tested. More threshold decay than this was classified as abnormal adaptation and occurred for at least 1 frequency in 38 ears involving 24 subjects,[1] i.e., there were 14 individuals with excess threshold tone decay bilaterally and 10 with excess decay in 1 ear. Via 20 of these ears, the adaptation elicited by the Carhart procedure was complete, i.e., beyond the limits of the test equipment. Of particular note is the fact that of the 12 subjects with complete tone decay 8 had bilaterally complete tone decay.

All of the 18 ears with maximum threshold adaptation greater than 30 dB but not greater than 65 dB (and not exceeding the equipment limits) had thresholds of 35 dB or less at the frequencies with maximum decay, i.e., none had more than a mild loss of threshold sensitivity. All of the remaining 20 ears with abnormally large amounts of threshold tone decay had complete decay at 1 frequency or more. For 15 ears, the distance between threshold and the equipment limits was from 35–65 dB. Thresholds in these ears were: 0–25 dB for 6 ears, 30–35 dB for 7 ears, and 40–65 dB for 2 ears. Complete threshold tone decay in the other 5 ears meant decay exceeding 65 dB: 4 of these ears had thresholds of 0–25 dB and 1 of 30–35 dB.

5. *Békésy audiometry*

Fixed frequency Békésy audiometry administered to 115 ears, produced Type I traces via 34 ears. Type II traces emerged 62 times, Type III traces twice, and Type IV traces 17 times.

One of the interesting features of the Békésy data was the incidence of ongoing adaptation for the continuous tone threshold. Such "threshold drift" occurred in about half the tracings characterized as Type II and in about 70 % of

Significant tone-to-noise perversion (Parker et al. 1968) was not seen in this sample even though it was actively sought.

[1] There were 5 other ears showing decay beyond the equipment limits, but with overall measurable shifts of 20 dB or less. These ears must be classified as having an undetermined amount of threshold tone decay.

category to be irregular enough to be classified in a *configurational* category other than the flat category It turned out that 36 of the 58 audiograms of normal ears were flat and un remarkable The other 22 audiometric configurations grouped themselves as follows 11 arched configurations 7 rising configurations, and 4 notched configurations (3 of them below 3 000 Hz) Thus, the preponderance of normal but irregular audiograms was characterized by slightly poorer thresholds for low frequencies than for either mid or high frequencies Air and bone conduction curves were interweaving for all of these cases

The audiometric patterns from the 64 ears exhibiting hearing losses were classified as fol lows when the severity of loss is categorized by the worst pure tone threshold in this scheme the term "mild reflects thresholds of 30 or 35 dB hearing level the label "moderate represents thresholds from 40 to 65 dB HL, and the term severe is used to classify thresholds in excess of 65 dB

1 arched 17 ears—7 mild 5 moderate 5 severe
2. gradually falling 12 ears—5 mild 3 moderate, 4 severe
3 sharply falling 1 ear—moderate
4 flat 3 ears—2 mild 1 severe
5 notched—below 3 000 Hz 5 ears—mild notched—at 3 000 Hz or higher 9 ears—4 mild 3 moderate 2 severe
6 high frequency loss at 3 000 Hz or higher 9 ears—8 mild 1 moderate
7 rising 8 ears–mild

Considering the threshold configurations from all 122 ears together the distribution of audiometric contours was (1) arched—28 ears (2) gradually falling—12 ears (3) sharply falling—1 ear (4) flat—39 ears (5) notched below 3 000 Hz—8 ears notched at 3 000 Hz or higher—10 ears (6) high frequency loss at 3 000 Hz or higher—9 ears and (7) rising—15 ears.

Thus, in this sample of 61 subjects, high frequency drop-off with or without low frequency involvement, was most common However a substantial fraction showed poorer thresholds for low than for mid frequencies. Moreover the arched pattern, not common in other populations appeared in 28 ears

Another way of viewing the audiometric findings is to consider the sensitivity exhibited in the so-called speech range (500–2 000 Hz) The next column in this table (column 7) reports by ear the pure tone averages across this range As one would expect from the review of audiometric configurations and thresholds, the preponderant majority of these 61 multiple sclerotic subjects showed good hearing across this range. Specifically only 15 of the 122 ears tested had pure tone averages for 500–2 000 Hz which exceeded 25 dB HL and only 4 ears had average hearing levels of 40 dB or poorer

2 *Speech reception thresholds*

Another conventional index of general auditory sensitivity is the speech reception threshold (SRT) Such thresholds were obtained for 121 ears (One subject would not tolerate suprathreshold testing through 1 ear) In only 6 instances (ears) did the speech reception threshold exceed 25 dB and in only 2 was it 40 dB or poorer

3 *Speech discrimination scores*

Discrimination for phonemically balanced monosyllables (NU 6) in a quiet situation at 40 dB SL was measured via 121 ears. In only 9 instances were the resultant scores below the 90% correct level

The competing message test was administered to 54 subjects (108 ears) In this test monosyllables were delivered to 1 ear at a sensation level of 50 dB re its SRT and sentences were delivered to the other ear at 60 dB sensation level re its SRT i e a signal/competition (S/C) ratio of −10 dB at opposite ears Normal listeners, when confronted by these conditions achieve scores from 90–100 %, that is, they duplicate their scores in quiet Scores less than 90 % correct were attained only 15 out of 108 times. Discrimination scores in quiet were also reduced via 7 of these ears, and for 4 of them, the presence of a contralateral competing message further

he 2-letter code used for SBMPL, the first letter always represents the relationship between thresholds in the 2 ears. As before, (E) stands for equal thresholds (within 10 dB) and (U) stands for unequal ones (>10 dB). The second letter of the code gives information about the localization judgment itself namely whether a midline experience was achieved at equal (E) intensities to the ears, at unequal (U) intensities to the ears, or whether the subject failed (F) to secure a median plane localization. The SBMPL results are recorded in the right ear row but pertain to both ears.

The results for the 60 persons to whom the SBMPL test was administered were as follows EE 38 EU-5, EF 5 UE 10 UU-2, and UF-0. Of special interest, of course, were the 10 individuals with similar thresholds in the 2 ears who could achieve no midline experience or achieved said experience with unequal intensities at the ears and the 2 individuals with unequal thresholds who achieved said experience with different intensities at the 2 ears.

9 *Masking level differences (MLDs)*

MLDs were obtained for conditions utilizing both 500 Hz tones and spondaic words as the test stimuli. Recall that the masking level difference was secured by comparing the amount of masking produced at 500 Hz or for spondees by noise (narrow band noise, 80 dB SPL overall level, for 500 Hz, wide band noise 80 dB SPL overall level for spondees) under 2 conditions (1) with the noise in phase with itself and the test stimulus in phase with itself at the 2 ears (S_0N_0), versus (2) with the noise in phase with itself but the test stimulus 180 out of phase with itself at the ears ($S_\pi N_0$).

One column of Table III gives the MLDs in dB for 500 Hz and the next for spondees. Twenty three of these subjects (almost half) had MLDs at 500 Hz of 7 dB or less. These results must be judged as abnormal since 95 of the control population (50 normal hearers) on which the test as calibrated had MLDs of 8 dB or more (mean 11 2 dB). Forty-two subjects took the spondee MLD test. Five-sevenths of them (30 persons) achieved MLDs of 5 dB or less. These MLDs must also be considered abnormally small since 95% of the control population obtained MLDs greater than 5 dB (mean = 8 7 dB). Therefore the 2 masking level difference tests proved to be items on which unusual auditory performance was quite consistently exhibited by the multiple sclerotic subjects under study.

B. Relationships among audiological results

The individual performances of the 61 multiple sclerotic patients shown in Table III revealed various permutations among test results. A topic of primary interest was that of determining what clustering of performances characterized the data for the entire group. Table IV supplies information on this topic. This table presents 776 comparisons in the form of fractions. The denominator indicates the number of instances under consideration at the moment. The numerator reports the number exhibiting the performance trait in question.

This method is used to report 2 sets of relationships. The 29 italicized fractions indicate the number of times that a single test was given (denominator) and the instances among these where performance was noteworthy (numerator)[1]. For example, the italicized ratio in Row 1 reveals that 15 *ears of the* 122 ears tested had PTAs exceeding 25 dB, in Row 2 that 6 ears of 121 ears tested had SRTs exceeding 25 dB etc. The remaining 749 fractions show the degree to which noteworthy results appeared concurrently on 2 tests. The *denominator* reports the instances in which a patient who showed *noteworthy* results for 1 test (indicated by the *row*) also took the second test (indicated by the *column*). The numerator designates the *number* (of such instances) where behavior was also noteworthy on the second test. For example, in Row 1 note that of the 15 ears with PTAs exceeding 25 dB SRTs were also obtained from 14 of them, and 6

1 In some instances, the numerator indicates a specific pattern of response, such as a Type I Békésy tracing, rather than an abnormal response.

those classified as Type IV traces. In such instances, the separation between the interrupted and continuous tone thresholds usually increased steadily as a function of time up to the maximum 3 minute test limit In the case of the Type II classification the separation of the tracings for the interrupted and continuous tones did not exceed 20 dB over the 3 minute time period whereas a separation in excess of 20 dB was observed for those tracings labelled Type IV

6 Short increment sensitivity index (SISI)

In Table III scores on the SISI task are divided into 3 groups according to the type of responsiveness shown As with other tests, what is reported in the table is the most revealing response when more than 1 type was given at different test frequencies via the same ear by the same subject A score of 60 correct or better for 1 dB increments at 20 dB SL was classified as evidencing increased sensitivity and was coded (I) Fourteen ears (of the 117 ears tested) achieved such scores. A normal (N) score indicates less than 60% correct responsiveness to 1 dB increments at 20 dB SL and 60% or higher correct responses at 85 dB HL when threshold sensitivity was 35 dB or better Fifty-one ears allowed scores of this sort A classification of decreased sensitivity (D) was assigned to ears which could not recognize greater than 1 dB increments at 20 dB SL and/or could not correctly recognize 55% or more of the 1 dB increments at 85 dB HL. Fifty two ears fell into this category on the SISI test

7 Alternate binaural loudness balance (ABLB)

The results of the ABLB task are shown for each person in Table III in terms of the following 2 letter codes The first letter of each pair gives information about thresholds in the 2 ears, namely whether they were equal (E—within 10 dB) or unequal (U—greater than 10 dB disparity) The second letter gives information about the intensity levels at which equal loudness was experienced namely whether such levels suggested recruitment (R) when the thresholds were unequal (U) decruitment (D) when the thresholds were equal (E) or unequal (U), no recruitment (N) when thresholds were unequal (U) or whether the intensity levels producing equal loudness were equal (E) when the thresholds were equal (E) All combinations but EE were placed in the row of results for the ear in which the pertinent loudness experience was judged to occur i e recruitment, decruitment and no recruitment were assigned to a particular ear When equal loudness was experienced at equal intensities in ears with equal thresholds (EE), the 2 letter code was placed in the right ear row but pertains to both ears.

Recruitment and no recruitment were defined according to the criteria suggested by Jerger (1962) Decruitment was defined as an abnormally slow rate of loudness growth in an ear whose threshold was 25 dB or better and whose threshold was similar to that of the ear against which the balance was performed Specifically when the achievement of equal loudness in ears with similar and normal thresholds required more than 10 dB greater intensity in 1 of those ears, the ear needing the additional intensity was assumed to be decruiting (see Davis & Goodman 1966) The opposite hypothesis, that the other ear was recruiting despite its normal threshold was rejected as untenable because it is less likely that at high signal levels, the stimulus to this other ear was abnormally loud than it is that the stimulus to the first ear was perceived at reduced loudness

Thirty seven persons with equal thresholds judged equally intense tones to be equally loud 11 others, however behaved in a manner suggesting decruitment in 1 of the ears Eleven persons had different thresholds in the 2 ears at the test frequencies 8 of these showed recruitment and 3 showed no recruitment Two persons could not be tested

8 Simultaneous binaural median plane localization (SBMPL)

The SBMPL test was administered to 60 persons and the results are reported in Table III by means of a system of coding the results that is similar to the one used for the ABLB test In

...patients with multiple sclerosis

SI			ABLB					SBMPL						500 Hz MLD < 8 dB	Speech MLD < 6 dB
Increased	Decreased	Normal	EE	ED	UR	UD	UN	EB	EU	EF	UE	UU	UP		
5 13	6/13	2/13	3/9	0/9	4/9		2/9	1/9	1/9	1/9	5/9	1/9		5/8	5/5
1 5	4/5	0 5	1/4	0,4	_/4		1/4	0/4	1/4	0/4	2/4	1/4		3/3	2/2
9	7 9	0 7	2/6	2/6	2/6		0/6	2/6	1/6	1/6	2/6	0,6		5/5	4/4
15	13/15	0,15	7/10	1/10	1/10		1/10	5/11	2/11	1/11	3/11	0/11		7/9	8/8
5/28	20 28	3/28	9,16	4/16	2/16		1/16	10/16	2/16	1/16	3/16	0/16		6/8	7/9
1 9	5 9	3 9	5/8	2/8	1/8		0/8	6/9	0/9	1/9	1/9	1/9		6/8	7/8
1 9	6 9	2,9	6/7	1/7	0/7		0/7	5/7	0/7	1/7	1/7	0/7		3/6	4/4
8 79	30 79	41/79	34/36	5/36	5/36		_/36	25/37	3/37	2/37	5/37	2/37		15/31	19/29
6 38	22,38	10,38	13/23	6/23	3/23		1/23	13/23	2/23	3/23	5/23	0/23		8/16	11/13
33	13 33	18/33	11/14	2/14	1/14		0,14	10/14	1/14	_/14	0/14	1/14		4/9	9/9
11 60	20 60	29 60	20/31	4/31	6/31		1/31	21/32	2/32	2/32	7/32	0/32		12/26	13/25
0 2	2/2	0/2	0/1	1/1	0/1		0/1	0/1	1/1	0/1	0/1	0/1		1/1	1/1
1/17	14 17	2/17	5/10	4/10	1/10		0/10	6/10	1/10	1/10	2/10	0/10		5/7	6/6
14/117			3/8	0,8	5/8		0/8	3/8	0/8	0/8	5/8	0/8		5/7	4/5
	52/117		20/79	6/29	1/29		_/29	18/30	5/30	3/10	3/30	1/30		12/21	13/17
		31/117	13/21	5/21	2/21		1/71	16/21	0/21	2/21	2/21	1/21		5/18	12/18
3 36	20 36	13/36	*37/59*					30/37	3/37	4/37	0/37	0/37		11/28	19/28
0 11	6 11	5/11		*11/59*				8/11	2/11	1/11	0/11	0/11		6/9	7/8
5 8	1 8	_8			*8/59*			0,8	0,8	0 8	7/8	1/8		4/6	3/5
						0/59									
0 3	2,3	1/3					*3 59*	0/3	0/3	0/3	2/3	1/3		1/2	0,0
3 37	18 37	16 37	30 38	8/38	0 38		0/38	*38,60*						11/36	19/27
0 5	5/5	0 5	3 5	/5	0/5		0/5		*5/60*					4/4	5/5
0 5	3 5	_/5	4 5	1 5	0 5		0/5			*5/60*				2,4	2/3
5/10	3 10	_/10	0 9	0 9	7/9		_/9				*10/60*			4/7	3/5
0	1	1 2	0	0 2	1/?		1/2					*2/60*		2/2	1/1
													0/60		
5 22	12 22	5/22	11 22	6/22	4/22		1/22	11/23	4/23	2/23	4/23	2/23		*23/47*	19/21
4 29	13 29	1 29	19 29	7 29	3/29		0,29	19 30	5/30	2/30	3/30	1/30		19/28	*30/42*

In all rows and columns except those for ABLB, SBMPL, and MLD results, N number of ears tested In the ABLB, SBMPL, and MLD rows and columns, N number of persons tested The table is most easily read by row The coding in the column and row headings is done in the same manner as explained in the text and detailed in footnotes to Table III.

The italicized fraction in each row is the ratio of abnormal or otherwise noteworthy results for the indicated test to the sample size for that test The other fractions in each row give incidences of noteworthy results on pairs of tests These other fractions are based on the number of noteworthy results (numerator) in the italicized ratio I the remainder of the ratios answer the question "Of the ears that yielded noteworthy results on test X, how many also yielded noteworthy results on test Y?" Of course, the denominator of these ratios does not always reflect the total number who performed in noteworthy fashion on test X, since some of them were not administered test Y

For example, in the first row PTAs were established for 122 ears and were abnormal (exceeded 25 dB) in 15 of the 122 ears (the italicized ratio). Continuing in the first row the remaining ratios are concerned only with these 15 abnormal ears and are read as follow SRT were obtained from 14 of the 15 ears, and for 6 of the 14, the SRT was also abnormal (exceeded 25 dB) Still in Row 1 note that discrimination for speech was tested in 14 of the 15 ears of interest, and that 4 of the 14 had scores below 90 %. Moving to Row 9 (tone decay 30 dB), observe that threshold tone decay exceeded 30 dB of the 120 ears tested (the italicized ratio in Row 9). The rest of the ratios in Row 9 deal only with the 38 ears with tone decay 8 of 38 had PTAs 25 dB, 1 of 38 had an SRT > 25 dB, etc.

Table IV *Incidence of noteworthy auditory test results and pairs of abnormal auditory test results for 61*

	PTA > 25 dB	SRT > 25 dB	Speech discrimination < 90 %	Competing speech < 90 %	Speech in white noise < 60 %	Speech in white noise dif bet. ears > 10 %	Filtered speech abnormal	Tone decay < 30 dB	Tone decay > 30 dB	Békésy Type I	Békésy Type II	Békésy Type III	Békésy Type IV
PTA > 25 dB	*15/122*	6/14	4/14	3/10	3/11	1/8	1/5	11/13	_/13	4/1	8/1	0 1	0 1
SRT 25 dB	6/6	*6/121*	3/6	_/2	2/3	0/3	0,0	4/5	1/5	0,4	4/4	0 4	0 4
Speech disc. < 90	4/9	3/9	*9/121*	7/7	8/8	0 6	2/3	5/9	4/9	0 9	7/9	0,9	_/9
Competing < 90 %	3/15	2/15	7/15	*15/108*	13/15	1/1	5/10	6/15	9/15	0,14	9 14	0,14	5/14
Speech in white noise < 60	3/28	_/28	8/28	13/25	*28/115*	17/19	4/13	12/28	16/28	1/?6	16/?6	1/?6	8/?6
Difference > 10 %	1/9	0/9	0/9	1/9	0/9	*9/57*	3/6	7/9	_/9	4/9	3/9	0 9	_/9
Filtered abnormal	1/9	0/9	2/9	5/9	4/9	3/9	*9/72*	6/9	3/9	_/9	6/9	0/9	1/9
Tone decay < 30 dB	11/8_	4/82	5/82	6/76	12/80	7/80	6/50	*82/1?0*		3_/79	45/79	0'79	_/79
Tone decay > 30 dB	2/38	1/38	4/38	9/32	16/35	_/35	3/22		*38/1?0*	_/36	17/36	_/36	15/36
Békésy													
Type I	4/34	0/34	0/34	0/34	0/34	4/34	2/22	3_/34	_/34	*34/115*			
Type II	8/62	4/6_	2/6_	10/36	16/58	3/58	6/37	45/6_	17/6_		*62/115*		
Type III	0/?	0/2	0/2	0/?	1/?	0/2	0/2	0/2	2/2			*2/115*	
Type IV	0/17	0/17	2/17	5/12	8/16	2/16	1/8	2/17	15/17				*17/115*
SISI													
Increased	5/14	1/14	2/14	2/11	5/12	1/12	1/7	8/14	6/14	_/14	11/14	0/14	1/14
Decreased	6/5?	4/52	7/52	13/48	20/51	5/51	6/30	30/52	22/5?	13/49	20/49	_/49	14/49
Normal	2/51	0/51	0/51	0,47	3/50	3/50	2/32	41/51	10/51	18/49	?9/49	0,49	2/49
ABLB													
EE	3/37	1/37	_/37	7/37	9/37	5/37	6/25	24/37	13/37	11/36	?0/36	0/36	5/36
ED	0/11	0/11	2/11	1/9	4/11	2/11	1/4	5/11	6/11	2/11	4/11	1/11	4/11
UR	4/8	2/8	_/8	1/5	2/5	1/5	0,5	5/8	3/8	1/8	6/8	0/8	1/8
UD													
UN	2/3	1/3	0/3	1/?	1/3	0/3	0/1	2/3	1/3	0/1	1/1	0/1	0/1
SBMPL													
EE	1/38	0/38	_/38	5/36	10/38	6/38	5/24	25/38	13/38	10/37	21/37	0,37	6/37
EU	1/5	1/5	1/5	2/3	2/5	0/5	0/3	3/5	_/5	1/5	_/5	1/5	1/5
EF	1/5	0/5	1/5	1/5	1/5	1/5	1/3	_/5	3/5	2/5	_/5	0,5	1/5
UE	5/10	_/10	2/10	3/7	3/7	1/10	1/6	5/10	5/10	0/9	7/9	0/9	_/9
UU	1/2	1/2	0/2	0/1	0/2	1/2	0/1	2/?	0/2	1/1	0 1	0 1	0/2
UF													
500 Hz MLD < 8 dB	5/23	3/23	5/23	7/?1	6/22	6/22	3/12	15/23	8/23	4/22	1_/22	1/2_	5/2_
Speech MLD < 6 dB	5/30	_/30	4/30	8/?9	7/29	7/29	4/14	19/30	11/30	9/29	13/?9	1/29	6/?9

of these 14 had SRTs exceeding 25 dB in Row 2, note that of the 6 ears with SRTs exceeding 25 dB all were administered speech discrimination tests, and 3 of the 6 correctly discriminated less than 90 of the test items etc

Table V presents the same information as Table IV except that the data were converted to percentages Table IV was retained to provide the sample size for each category Table V gives percentages for ease of discussion and review later in the text

The relationships thus revealed which seemed to the writers to be most noteworthy are discussed below but the reader may find others that he feels are of special significance

patients with multiple sclerosis

SISI			ABLB					SBMPL						500 Hz MLD < 8 dB	Speech MLD 6 dB
Increased	Decreased	Normal	EE	ED	UE	UD	UN	EE	EU	EF	UE	UU	UF		
5/13	6/13	-/13	3/9	0,9	4/9		2/9	1/9	1/9	1/9	3/9	1/9		5/8	5/5
1/3	4/5	0 5	1/4	0 4	2/4		1/4	0 4	1/4	0/4	-/4	1/4		3/3	2/2
9	7/9	0/7	2/6	/6	2/6		0/6	2/6	1/6	1/6	2/6	0 6		5/5	4/4
2/15	13/15	0/15	7/10	1/10	1/10		1/10	5/11	2/11	1/11	3/11	0/11		7/9	8/8
5/28	20 28	3/28	9/16	4/16	2/16		1/16	10/16	2/16	1/16	3/16	0/16		6/8	7/9
1/9	5/9	3,9	5/8	2/8	1/8		0/8	6/9	0,9	1/9	1/9	1/9		6/8	7/8
1/9	6 9	2 9	6/7	1/7	0/7		0/7	5/7	0/7	1/7	1/7	0/7		3/6	4/4
8/79	30/79	41/79	24/36	5/36	5/36		2/36	25/37	3/37	2/37	5/37	2/37		13/31	19/29
6/38	22/38	10,38	13/21	6/23	3/23		1/23	13/23	2/23	3/23	5/23	0/23		8/16	11/13
2/33	13/33	18/33	11/14	2/14	1/14		0/14	10/14	1/14	2/14	0/14	1/14		4/9	9 9
11 60	20 60	29 60	20/31	4/31	6/31		1/31	1/32	2/32	2/32	7/32	0 32		12/26	13/25
8	1/2	0 2	0 1	1/1	0/1		0,1	0/1	1/1	0/1	0/1	0,1		1/1	1/1
1 17	14/17	2 17	3/10	4 10	1/10		0/10	6/10	1/10	1/10	2/10	0/10		5/7	6 6
14/117			3/8	0 8	5/8		0,8	3/8	0/8	0/8	5/8	0,8		5/7	4 5
	52/117		20/29	6 29	1/29		2/29	18/30	5/30	3/30	3/30	1/30		12/21	13/17
		51/117	13/21	5/21	2/21		1/71	16/21	0/21	2/21	2/21	1/21		5/18	1_/18
3 36	20 36	13/36	*37/59*					30/37	3/37	4/37	0/37	0/37		11/28	19/28
0 11	6 11	3/11		*11/59*				8/11	2/11	1/11	0,11	0,11		6/9	7 8
5 8	1 8	2 8			*8/59*			0,8	0,8	0 8	7 8	1/8		4/6	3/5
						0/59									
0 3	2 3	1/3					*3/59*	0,3	0 3	0/3	-/3	1/3		1 2	0 0
3 37	18 37	16/37	30 38	8/38	0 38		0,38	*37/60*						11/36	19/27
0 5	3 5	0 5	3 5	2 5	0/5		0/5		*5/60*					4/4	5/5
0 5	3 5	5	4 5	1 5	0/5		0 5			*5/60*				2/4	-/3
3 10	3 10	2/10	0 9	0 9	7 9		2/9				*10/60*			4/7	3/5
0	1 2	1 2	0 2	0 2	1/2		1/2					*2/60*		2/2	1/1
													0/60		
5 22	12 22	5 22	11 22	6 22	4 22		1/22	11/23	4/23	-/23	4/23	-/23		*23/47*	19 21
4 29	13 29	1 29	19 29	7 29	3/29		0 29	19 30	3/30	2/30	3/30	1/30		19/28	*38/42*

In all rows and columns except those for ABLB, SBMPL, and MLD results, N = number of ears tested. In the ABLB, SBMPL, and MLD rows and columns, N = number of persons tested. The table is most easily read by rows. The coding in the column and row headings is done in the same manner as explained in the text and detailed in footnotes to Table III.

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For example, in the first row, PTAs were established for 122 ears and were abnormal (exceeded 25 dB) in 15 of the 122 ears (the italicized ratio). Continuing in the first row, the remaining ratios are concerned only with these 15 abnormal ears and are read as follows: SRTs were obtained from 14 of the 15 ears, and for 6 of the 14, the SRT was also abnormal (exceeded 25 dB). Still in Row 1, note that discrimination for speech was tested in 14 of the 15 ears of interest, and that 4 of the 14 had scores below 90 %. Moving to Row 9 (tone decay > 30 dB), observe that threshold tone decay exceeded 30 dB in 38 of the 120 ears tested (the italicized ratio in Row 9). The rest of the ratios in Row 9 deal only with the 38 ears with excess tone decay, i.e. 2 of 38 had PTA > 25 dB, 1 of 38 had an SRT > 25 dB, etc.

Table V *Incidence (percentage) of abnormal auditory test results and pairs of abnormal auditory test results for 61 patients with multiple sclerosis*

	PTA > 25 dB	SRT > 25 dB	Speech discrimination < 90	Competing speech < 90	Speech in white noise < 60	Speech in white noise, difference between ears > 10	Filtered speech abnormal	Tone decay < 30 dB	Tone decay > 30 dB	Békésy Type I	Békésy Type II	Békésy Type III	Békésy Type IV	SISI Increased	SISI Decreased	SISI Normal	ABLB EE	ABLB ED	ABLB UR	ABLB UD	ABLB UN	SBMPL EE	SBMPL EU	SBMPL EF	SBMPL UE	SBMPL UU	SBMPL UF	500 Hz MLD < 8 dB	Speech MLD < 6 dB
PTA > 25 dB	12	43	29	30	27	12	20	85	15	33	67	0	0	38	46	15	33	0	44		22	11	11	11	56	11		62	100
SRT > 25 dB	100	5	50	100	67	0	0	80	20	0	100	0	0	20	80	0	⌐5	0	50		25	0	25	0	50	25		100	100
Speech disc < 90	44	33	7	100	100	0	67	56	44	0	78	0	22	22	78	0	33	33	33		0	33	16	16	33	0		100	100
Competing speech < 90 %	20	13	46	14	86	8	50	40	60	0	64	0	36	13	86	0	70	10	10		10	45	18	9	27	0		78	100
Speech in white noise < 60 %	11	7	⌐8	52	24	89	30	43	57	4	62	4	30	18	71	10	56	25	12		6	62	12	6	18	0		75	78
Difference 10 %	11	0	0	11	0	16	50	78	22	44	33	0	22	11	56	33	62	25	12		0	67	0	11	11	11		75	88
Filtered abnormal	11	0	22	56	44	33	12	67	33	22	67	0	11	11	67	22	86	14	0		0	71	0	14	14	0		50	100
Tone decay 30 dB	13	4	6	8	15	8	12	68		40	57	0	3	10	38	51	66	14	14		6	68	8	5	14	5		48	66
Tone decay 30 dB	5		10	28	46	6	14		32	6	47	6	42	16	58	26	56	26	13		4	56	8	13	22	0		50	84
Békésy																													
Type I	12	0	0	0	0	12	9	94	6	30				6	39	54	78	14	7		0	71	7	14	0	7		44	100
Type II	13	6	3	18	28	5	16	73	27		54			18	33	48	64	12	19		3	66	6	6	22	0		46	52
Type III	0	0	0	0	50	0	0	0	100			2		0	100	0	0	100	0		0	0	100	0	0	0		100	100
Type IV	0	0	12	42	50	12	12	12	88				15	6	82	1⌐	50	40	10		0	60	10	10	20	0		71	100
SISI																													
Increased	36	7	14	18	42	8	14	57	43	14	78	0	7	12			38	0	62		0	38	0	0	62	0		71	80
Decreased	1	7	13	27	39	10	20	58	42	26	40	4	28		44		69	20	3		7	60	16	10	10	3		57	76
Normal	4	0	0	0	6	6	6	80	20	36	59	0	4			44	62	24	10		4	76	0	10	10	4		28	67
ABLB																													
EE	8	2	5	18	24	14	24	65	35	30	56	0	14	8	56	36	63					81	8	10	0	0		39	68
ED	0	0	18	11	36	18	25	45	55	18	36	9	36	0	54	45		19				73	18	9	0	0		67	88
UR	50	25	25	20	40	20	0	62	38	12	75	0	12	62	12	25			14			0	0	0	88	12		67	60
UD																				0									
UN	67	33	0	50	33	0	0	67	33	0	100	0	0	0	67	33					5	0	0	0	66	33		50	0
SBMPL																													
EE	2	0	5	14	⌐6	16	20	66	34	27	56	0	16	8	48	43	78	21	0		0	63						30	70
EU	20	20	20	67	40	0	0	60	40	20	40	20	20	0	100	0	60	40	0		0		8					100	100
EF	20	0	20	20	20	20	33	40	60	40	40	0	20	0	60	40	80	20	0		0			8				50	67
UE	50	20	20	42	42	10	16	50	50	0	78	0	22	50	30	20	0	0	78		22				17			57	60
UU	40	50	0	0	0	50	0	100	0	100	0	0	0	0	50	50	0	0	50		50					3		100	100
UF																											0		
500 Hz MLD < 8 dB	22	13	22	33	27	27	25	65	35	18	55	4	23	23	54	23	50	77	18		4	48	17	8	17	8		49	90
Speech MLD 6 dB	17	6	13	28	24	24	78	63	37	31	44	4	20	14	44	41	66	24	10		0	63	17	7	10	3		68	71

The percentages given [illegible] derived from the fractions in T[illegible]ble IV. See the footnotes in T[illegible]ble IV [illegible] the text for explanation of the difference between [illegible] and non-italicized fractions [illegible] the manner in which [illegible] table can be read. See T[illegible]ble [illegible] for [illegible] the [illegible] and row headings.

1 *Pure tone hearing loss*

Marked pure tone hearing loss was not common in this population It was mentioned earlier that fully 60 % of the ears tested had no pure tone loss exceeding 35 dB, i.e. exceeding a mild hearing loss. Furthermore, 88 % had pure tone averages (PTAs) of 25 dB or better Interestingly of those multiple sclerosis patients with some hearing loss, 57 % had deficits which were bilateral.

Of the ears with PTAs exceeding 25 dB half had equally deficient SRTs, but few had discrimination for speech in quiet below 90 correct. Most of the special speech and tonal test results for ears with PTAs > 25 dB were not those classically associated with retrocochlear lesion to illustrate, in most cases tone decay was minimal, loudness balancing demonstrated either equal rates of loudness growth or recruitment, median plane localization was achieved at equal intensity levels to the ears, Békésy traces were Type II, and so on However it would be a mistake, as is discussed later to assume that these findings suggested in all these cases that there was a coincident lesion which affected auditory responsiveness, but was unrelated to multiple sclerosis

2 *Speech discrimination*

Traditional speech testing, the determination of SRTs and of discrimination for monosyllables in q iet settings, revealed so little abnormality (only 5 of the SRTs were greater than 25 dB and only 7 of the speech discrimination scores ere below 90 correct) that analysis of concurrent deficits on other tests is in many instances meaningless However 2 points of importance can be established All ears with SRTs 25 dB also had PTAs 25 dB Most also performed poorly on other special peech tests

Competing message test scores were below 90 correct for 14 of the ears tested, even though PTAs and SRTs were almost never abnormal Furthermore, in half the instances in which the competing message scores were decreased speech discrimination in quiet was normal In almost all cases of poor performance on the competing message task, difficulty was also encountered on the speech in white noise test. Breakdown also occurred half the time during filtered speech testing. These ears were further characterized by abnormal threshold adaptation, decreased SISI scores, and abnormally small MLDs. Of potential special interest in this group of results were those 8 occasions when there was breakdown on the competing message task even though speech discrimination in quiet was normal These latter cases were characterized by the same pattern of test results as those just detailed for the entire group.[1]

Discrimination scores for speech in white noise were less than 60 % for one-fourth of the ears tested. In addition, 16 % of the time, scores differed by more than 10 % between the 2 ears of the subjects. Thus, in total, 40 % of the ears tested were unable to deal normally with speech when noise was simultaneously presented to the same ear In terms of total number then, performance on this test was the most frequently defective of all the monaural speech tests as well as 1 of the most frequently abnormal of all tests. When reduced speech in white noise scores were obtained, PTAs or SRTs rarely exceeded 25 dB and only 28 of the time was the speech discrimination score in quiet less than 90 %. The most common abnormal results to occur in combination with reduced speech in white noise scores were unusual adaptation, decreased SISI scores, and reduced MLDs. In addition, about half of these ears also performed poorly on competing message tasks and one-fourth exhibited decruitment. As a last comment, it is worth noting that although reduced speech in white noise scores usually occurred via ears which exhibited most of the pattern of results discussed above, in some instances such reduction was accompanied only by abnormal scores on other difficult speech tests and occasionally

1 many of the instances of breakdown on competing message tests, noise competition was substituted for the standard sentence material, g broad spectrum noise, speech spectrum noise, etc., at similar S C ratios. In all instances here this was done speech discrimination returned to the degree of excellence obtained in quiet settings.

by decruitment i e by signs of high level, CNS lesions

Filtered speech scores were abnormal for 12 % of the ears tested These cases were characterized by normal pure tone thresholds, speech reception thresholds and speech discrimination in quiet Breakdown also occurred half the time on other difficult speech tests when materials were presented through these ears Abnormal adaptation loudness balance or median plane localization results were not characteristic. Half of these subjects had pure tone MLDs smaller than 8 dB and all had abnormally small speech MLDs.

3 *Threshold tone decay*

Threshold tone decay exceeding 30 dB was exhibited via 32% of the ears tested Slightly over half of these instances represented adaptation beyond the equipment limits at some frequency More persons with tone decay had bilateral deficits than had unilateral ones, but almost none of the ears via which decay appeared had pure tone thresholds exceeding a mild loss of hearing, i e exceeding 35 dB The high incidence of threshold tone decay especially bilateral tone decay and the fact that almost never was marked pure tone hearing loss associated with such decay were 2 of the particularly interesting auditory characteristics of this multiple sclerosis population

Individuals exhibiting excess decay generally performed normally via the same ear on regular and filtered speech discrimination tests. In one fourth of these instances, scores below 90 % were obtained on the competing message task About half the time an abnormal number of monosyllables was misunderstood when noise was presented to the same ear On tonal tests subjects prone to excess threshold tone decay showed same ear adaptation on the Békésy task (about half giving Type II traces and about half giving Type IV traces) decreased responsiveness to SISI increments, a 30 % incidence of decruitment (when hearing sensitivity was normal bilaterally) or no recruitment (despite unilateral hearing loss) variable SBMPL results, a 50 in-cidence of reduced masking level differences at 500 Hz, and small MLDs for speech.

4 *Békésy audiometry*

Békésy audiometry also revealed auditory adaptation Of particular interest is the fact that 15 of the ears yielded Type IV tracings and that another 54% gave Type II traces For only 2 ears, 2% of the population were Type III tracings noted despite the fact that threshold tone decay beyond the equipment limits was much more common Half of the Type II and IV traces featured ongoing, gradual adaptation of the continuous tone threshold As was the case with the tone decay findings less than 10 of the ears with Type II III and IV Békésy traces had significant pure tone hearing loss.

In those instances where tracings were classified Type IV threshold tone decay exceeded 30 dB about 90% of the time Behavior on the speech tests and the other tonal tests was like that described for the ears with excess threshold tone decay

Type II Békésy traces were generally observed when PTAs, SRTs, and speech discrimination in quiet were normal In a significant percentage (33%) of the ears through which Type II traces were obtained the speech in white noise scores were reduced A smaller group experienced difficulty with competing message speech (18 %) One-fourth had excess tone decay and one half had reduced MLDs. Loudness balancing and median plane localization results were generally normal but the SISI results were mixed half were normal, one-third were decreased and one sixth were increased

Type I Békésy tracings were generally associated with normal auditory behavior on all but the MLD tests

5 *SISI*

Most SISI scores fell into the 2 categories of normal and decreased response in about equal numbers. Only 12 of the scores were classified as increased In all these latter instances the ears involved had thresholds exceeding 25 dB at

one frequency 7 had mild hearing losses, 5 respoke moderate losses, and 1 had a severe oss

The ears through which normal SISI scores were obtained, 44% of those tested, performed as follows on other tests PTAs and SRTs were 25 dB or better discrimination for monosyllables both in quiet and in difficult circumstances was normal 80% had tone decay less than 30 dB Békésy tracings were Type I or Type II median plane localization was achieved in a normal fashion, and pure tone MLDs were usually (7) normal. Interestingly one-fourth of the ears allowing normal SISI scores had decrutment (the rest balanced loudness equally) and two-thirds had reduced masking releases when spondees were the stimulus

When decreased scores on the SISI task were found (44 of the ears tested), more abnormal results were observed on other tests PTAs, SRTs, and speech discrimination in quiet were generally normal 27 performed abnormally in competing message situations 50 had difficulty interpreting speech in white noise 42 demonstrated threshold tone decay exceeding 30 dB and about 70 had Type II or Type IV Békésy tracings. Of the persons whose ears achieved decreased SISI scores, 27 revealed decrutment, 27 achieved midline images at unequal intensity levels or achieved no central image at all, over 57 had abnormally small MLDs at 500 Hz, and 76 had abnormally small MLDs for spondees

6 *ABLB*

Findings indicating decrutment (when both ears had normal and similar thresholds) or no recruitment (when there was a unilateral threshold deficit) were more common (24) than were results suggestive of recruitment (14) Decrutment was usually associated with abnormal performance on the speech in white noise test (54) threshold tone decay exceeding 30 dB (54), Type II or IV Békésy traces (77), and decreased SISI scores (54) Many of the persons with decrutment achieved normal midline experiences on the SBMPL task (73), but had abnormally small MLDs at 500 Hz (67%) and for speech (88%).

Although decrutment and reduced scores on competing message speech tests are both considered indicators of temporal lobe lesion (in the absence of evidence of more peripheral pathology) and although both occurred in about the same number of ears in this sample, the 2 findings as a combination were observed only twice

7 *SBMPL*

Of the 60 persons who were administered the SBMPL test, 80% had similar thresholds in the 2 ears for the frequencies tested Of these, 20% either could not achieve a midline image or achieved said image only when an interaural intensity difference that exceeded 10 dB was established All 12 persons with unequal thresholds at frequencies where the test was given achieved central images, 10 of them did so when equal intensities were delivered to both ears and 2 did so only when the stimuli were presented at different intensity levels to the 2 ears.

Persons who achieved a median plane experience when equally intense tones were delivered to their ears generally did well on regular pure tone and speech tests They also had little trouble with difficult speech tests, yielded Type II Békésy traces, had tone decay of 30 dB or less had normal or increased SISI scores (although 49 had decreased scores), judged equally intense tones as being equally loud, had normal pure tone MLDs, and yielded small speech MLDs.

Persons who did not experience a midline sensation or who did so only when tones of differing intensities were presented to the ears performed as follows on other tests. 20 had speech discrimination below 90% in quiet, 33 below 60 in noise 17 below 90 in a competing message situation, and 14 performed abnormally on the filtered speech test 43 had threshold tone decay exceeding 30 dB 36% yielded Type II Békésy tracings and 17 gave Type IV tracings 82 had decreased SISI scores 30 demonstrated decrutment or no recruitment 80 had unusually small MLDs for

by decruitment, i e by signs of high level CNS lesions.

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None of these had an associated spontaneous nystagmus. Three had a positional nystagmus, eyes closed, direction fixed, beating to the same side as the shift, and 3 other patients had a caloric directional preponderance, again to the same side as the shift. There were none with a positional nystagmus or directional preponderance beating away from the side of the shift.

2. *Slow tracking*

Forty percent of the patients showed abnormalities of tracking, either some irregularity, ataxia, or saccades.

3. *Pendulum tracking*

In this series, abnormalities of pendulum tracking were found in 55% of the individuals.

4. *Optokinetic nystagmus*

Fifty-five percent of the patients performed poorly on this test. In all instances of faulty tracking but 2, the abnormalities were bidirectional.

B. Spontaneous nystagmus, eyes closed

Thirty-three percent of the patients had a spontaneous nystagmus; in 9 instances the beating was to the left and in 5 cases, the direction of the nystagmus was to the right.

C. Positional nystagmus, eyes closed

Half of the 38 patients given this test were free from positional nystagmus. In the 19 instances where it occurred, it was direction-fixed 16 times and direction-changing 3 times.

D. Caloric tests

Evaluation of the maximum slow phase velocity, eyes closed, revealed a relative unilateral paresis in 41 % and a directional preponderance in 33 %. As evaluated by duration, eyes open, there was a unilateral paresis in 7 % and a directional preponderance in 11 %. (The latter two values are not shown in Table VI because of the infrequency of their occurrence.)

Caloric hyperexcitability as evaluated by the maximum slow phase velocity was seen in 48 % of the patients, being marked in 11%. When the durations were considered, there was a 14% incidence of hyperexcitability. (Again, the latter value is not given in Table VI.)

Dysrhythmia of the post-caloric nystagmus, usually most manifest with the eyes open, occurred for 34% of the subjects, and an impairment in attenuation of the nystagmus on opening the eyes during the caloric tests was found in 41%.

Triangular waves were seen in only 1 case in this series. (Absence of the fast phase of caloric nystagmus is sometimes associated with the medial longitudinal fasciculus syndrome, but no examples were encountered here.)

IV. SUMMARY

Neurological examinations of the 61 multiple sclerosis patients participating in this study revealed symptoms of widespread lesions throughout the central nervous system, particularly in the brainstem and adjacent midbrain regions. Comparison of this sample with others reported in the literature indicated that the present group was typical of the multiple sclerosis population.

Auditory evaluations, which included routine and current special auditory tests as well as some auditory tasks not heretofore employed clinically, demonstrated a marked diversity of auditory aberrations. These abnormalities were most commonly elicited by tests requiring response to a sustained stimulus, by tests requiring discrimination of speech in conditions other than quiet, and by binaural masking tests.

Vestibular examinations utilizing electronystagmography showed a variety of noteworthy results. Abnormal visually induced eye movements, positional nystagmus, and hyperexcitability in response to caloric stimulation were the most common findings.

500 Hz, and 89 % had unusually small MLDs for speech

8 *MLDs*

Recall that masking level differences were abnormally small at both 500 Hz and for spondees for a large proportion of this sample of multiple sclerosis patients 49 % of them yielded reduced MLDs at 500 Hz, 71 % attained reduced MLDs for spondaic words This rate of abnormality was one of the greatest for any of the auditory tests employed in the test battery

Fewer than 25 of the subjects with abnormally small MLDs at 500 Hz had PTAs or SRTs exceeding 25 dB Their speech discrimination in quiet was usually good but 33 % broke down in competing message situations and 54 % had difficulty with speech discrimination when noise was also present in the same ear About twice as many (65 % vs. 34 %) had 30 dB or less threshold tone decay as had decay greater than 30 dB About one-fourth of the persons with small pure tone MLDs had Type III or IV Békésy traces nearly half had Type II tracings SISI scores were mostly (54 %) decreased Loudness balancing yielded normal results for half the persons tested one-third showed decruitment or no recruitment and one-fifth exhibited recruitment SBMPL findings were unremarkable for half but two-fifths of the subjects could not achieve a midline image or did so in a manner suggesting faulty binaural processes. Finally 9 of every 10 persons with a small 500 Hz MLD also had a small speech MLD

The same general pattern that held for the 500 Hz MLD results vis a vis the other test findings also held for the speech MLD results. Of special interest are the facts that of the subjects yielding small speech MLDs, 27 % performed poorly on the SBMPL task and 68 % had small 500 Hz MLDs

III VESTIBULAR FINDINGS

Forty-four of the 61 patients in this study underwent the ENG examinations described earlier Almost all of these 44 patients took the entire battery although there were several instances where a few tests had to be omitted for such reasons as general debility of the patient or the status of the ear drum (thin scarred etc.). The results which are outlined in Table VI are reported as the respective percentages of abnormalities for patients given each test The general trends in these results are reviewed in a moment. For the reader who is interested a more detailed look at the vestibular findings for each patient is presented in Table III In this table readers can examine more carefully all the results for each patient. To facilitate such an examination, the vestibular signs presented in Table VI in the order they are listed have been assigned successive letters of the alphabet (A–K) Therefore, the column reporting these signs in Table III contains letters representing the appropriate sign (A) being indicative of abnormal optokinetic tracking and so on through (K) being representative of lateral gaze imbalance

Table VI *Incidence (percentage) of vestibular abnormalities for 44 patients with multiple sclerosis who were given ENG examinations*

The code designation was assigned to facilitate interpretation of Table III

Description	Per centage	Code designation
Abnormal optokinetic	55	A
Abnormal pendulum	55	B
Positional nystagmus	50	C
Hyperexcitability	48	D
Poor attenuation	41	E
Unilateral paresis	41	F
Abnormal slow tracking	40	G
Dysrhythmia	34	H
Spontaneous nystagmus	33	I
Directional preponderance	33	J
Lateral gaze imbalance	16	K

A. Visually induced eye movements

1 *Lateral gaze imbalance*

Only 16 of the patients had a shift of 10 or greater of the electrical axis of the eyes on changing from the eyes open, gaze ahead to the eyes closed gaze direction uncontrolled modality

None of these had an associated spontaneous nystagmus. Three had a positional nystagmus, eyes closed, direction fixed, beating to the same side as the shift, and 3 other patients had a caloric directional preponderance again to the same side as the shift. There were none with a positional nystagmus or directional preponderance beating away from the side of the shift.

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4 Discussion

I INTRODUCTION

The foregoing résumé of results emphasizes the complexity of the picture presented by the symptomatology of multiple sclerosis even when the individual fluctuations that occur with passing time are not included in the data As would be expected given the variability of multiple sclerosis consistent interrelations among symptoms do not always characterize the clinical population This complexity makes interpretation of results such as these very difficult. Nonetheless, trends appear which warrant analysis Therefore the task in this chapter is to interpret the trends that appeared in the audiological data and to relate them to the other findings at hand

The first fact to be borne in mind is that neurological examinations revealed most of our 61 subjects to have sclerotic involvement referable to the medulla and/or higher Thus, pathology at levels close to those occupied by the central auditory system had been indirectly demonstrated for many of these individuals and involvement of the central auditory system is a likelihood in some of them Second the authors re-emphasize that this population was typical of other multiple sclerosis populations discussed in the literature and that it was selected only on the basis of the certainty of diagnosis

One must also recall that the lesions of multiple sclerosis are limited to the central nervous system Thus while the most peripheral auditory lesion this disease can cause is in the root of the VIIIth nerve there is a series of more central and of higher level sites in the auditory system which may be involved In consequence of this consideration one must be cautious when interpreting audiological data not to jump too quickly to the assumption that the findings gathered here have the same meaning as they would have if they were the result of more peripheral causes, including VIIIth nerve tumors

One does well to remind himself that independently caused peripheral auditory lesions will be happenstance concomitants of multiple sclerosis in some cases but that these instances will not be frequent because multiple sclerotic patients are predominantly young adults. Study of the audiometric configurations, a detailed history and review of the medical records for each case convinced the authors that coincidental peripheral hearing involvements in this sample were rare One should of course, be on the lookout for such concomitance of pathology but one should also be ready to attribute a high prevalence of any auditory symptoms among multiple sclerosis patients to the neurological disorder rather than to an unusual concentration of such happenstances

The plan in this chapter is first to take a general look at some relationships between the auditory findings and other test results and then to look more specifically at each of the auditory tests.

II AUDITORY RESULTS IN RELATION TO NEUROLOGICAL FINDINGS

The incidence of cortical midbrain, and brain stem lesions in this particular population has been discussed in detail in Chapter 3 Each individual's profile of inferred neurological abnormalities has been carefully drawn in an attempt to establish the validity of the claim that the auditory results should be examined in light of known CNS damage It is abundantly evident that such damage did indeed exist in this sample given the incidence of MLF syndrome optic atrophy diplopia and oscillopsia and so on as detailed in Tables I and II

If one examines the incidence of abnormal auditory responsiveness as a function of the clinically inferred extent and level of neurological insult (as localized during neurological evaluations in the four general levels of the CNS portrayed in Fig. 8), it is quite clear that the extent of damage within the CNS has a demonstrable effect on the probability of abnormal auditory behavior. The main relationships are summarized in Table VII which gives the percentages of noteworthy auditory results associated with various combinations of inferred sites of lesion found in the population under study. Each percentage given in the table is the proportion of the patients given that test who exhibited the characteristic in question. Remember that not all subjects took every test. The neurological levels (1–4) referred to in the table are those defined and detailed in Fig. 8, Table II, and the discussions thereof. The grouping of levels into 4 general categories was necessary because sample size per category would otherwise have been too small, e.g., for this reason, all patients with signs thought referrable to Levels 1, 2, or 3 are in a single category. Recall, however, that population size for all combinations of neurological signs in this sample was given in Table II so that more specific comparisons can be made by referring to it.

The features of importance that emerge from Table VII are summarized below.

The incidence of auditory abnormalities cannot be attributed solely to lesions within the low brainstem, i.e. Level 4. For example, the typical auditory findings for the 8 persons with lesions only in Level 4 were normal pure tone and speech thresholds, no problems with difficult speech, normal SISI scores, normal loudness balancing, minimal adaptation in most instances, etc. The frequent observation of Type II Békésy tracings and reduced speech MLDs were the noteworthy findings for this subgroup. However, if one considers the 12 subjects with symptoms attributed to Level 4 and the (adjacent) midbrain, Levels 3 and sometimes 2, a higher incidence of abnormality was detected: 36 % had difficulty with speech in white noise, 50 % revealed threshold tone decay exceeding 30 dB, 4? % yielded Type II and 25 % Type IV Békésy traces, 50 % achieved low SISI scores, 41 % demonstrated decruitment (or no recruitment despite unilateral hearing loss), 56 % had abnormally small MLDs at 500 Hz, and 75 % obtained unusually small MLDs for spondees. Even more dramatic were the findings from the 12 individuals whose symptoms suggested lesions only at the midbrain or higher in the CNS, i.e., in Levels 1 and/or 2 and/or 3. This population had incidences of abnormality (as defined throughout the paper) for the indicated tests as follows: competing message speech—33 %, speech in white noise—40 %, filtered speech—50 %, excess threshold tone decay—64 %, Type II Békésy tracings—64 %, Type IV Békésy traces—18 %, decreased SISI scores—60 %, small 500 Hz pure tone MLDs—50 %, and small speech MLDs—83 %.

Widespread damage within the CNS, inferred from symptoms attributed to lesions in Levels 1, 2, 3 and 4, is more likely to result in auditory dysfunction than is spotty damage, i.e. lesions at non-adjacent levels such as Levels 1 and 3, 2 and 4, etc. For example, if one compares the 8 patients with lesions attributed to Levels 1–4 with those 14 with lesions at non-adjacent levels, auditory abnormality was much more prevalent in the group with widespread disorders: 38 % had pure tone averages exceeding 25 dB, 38 % could not correctly discriminate speech in quiet, 50 % had difficulty with competing speech messages, 50 % could not normally interpret filtered speech, 63 % erred excessively on speech in white noise, 50 % had excess threshold tone decay, 57 % gave Type II Békésy tracings, 29 % yielded Type IV Békésy traces, 63 % obtained decreased SISI scores, 38 % showed decruitment, 83 % had small pure tone MLDs, and 100 % had small speech MLDs. On the other hand, subjects with symptoms judged due to damage at scattered nonadjacent levels yielded incidences of abnormality exceeding 30 % on only the Békésy task (50 % Type II, 21 % Type IV), SISI test (64 % decreased), and speech MLD (64 % abnormally small).

Eight of the 61 multiple sclerotic patients in

4 Discussion

I INTRODUCTION

The foregoing resumé of results emphasizes the complexity of the picture presented by the symptomatology of multiple sclerosis even when the individual fluctuations that occur with passing time are not included in the data As would be expected given the variability of multiple sclerosis, consistent interrelations among symptoms do not always characterize the clinical population. This complexity makes interpretation of results such as these very difficult. Nonetheless trends appear which warrant analysis Therefore the task in this chapter is to interpret the trends that appeared in the audiological data *and to relate them to the other findings at hand*

The first fact to be borne in mind is that neurological examinations revealed most of our 61 subjects to have sclerotic involvement referrable to the medulla and/or higher Thus, pathology at levels close to those occupied by the central auditory system had been indirectly demonstrated for many of these individuals and involvement of the central auditory system is a likelihood in some of them Second the authors *re-emphasize that this population was typical* of other multiple sclerosis populations discussed in the literature and that it was selected only on the basis of the certainty of diagnosis.

One must also recall that the lesions of multiple sclerosis are limited to the central nervous system Thus, while the most peripheral auditory lesion this disease can cause is in *the root of the* VIIIth nerve there is a series of more central and of higher level sites in the auditory system which may be involved In consequence of this consideration one must be cautious when interpreting audiological data not to jump too quickly to the assumption that the findings gathered here have the same meaning as *they would have* if they were the result of more peripheral causes, including VIIIth nerve tumors

One does well to remind himself that independently caused peripheral auditory lesions will be happenstance concomitants of multiple sclerosis in some cases, but that these instances will not be frequent because multiple sclerotic patients are predominantly young adults. Study of the audiometric *configurations, a detailed* history and review of the medical records for each case convinced the authors that coincidental peripheral hearing involvements in this sample were rare One should of course be on the lookout for such concomitance of pathology but one should also be ready to attribute a high prevalence of any auditory symptoms among *multiple* sclerosis patients to the neurological disorder rather than to an unusual concentration of such happenstances

The plan in this chapter is first to take a general look at some relationships between the auditory findings and other test results, and then to look more specifically at each of the auditory tests

II AUDITORY RESULTS IN RELATION TO NEUROLOGICAL FINDINGS

The incidence of cortical midbrain and brainstem lesions in this particular population has been discussed in detail in Chapter 3 Each individual's profile of inferred neurological abnormalities *has been carefully drawn in an* attempt to establish the validity of the claim that the auditory results should be examined in light of known CNS damage It is abundantly evident that such damage did indeed exist in this sample given the incidence of MLF syndrome optic atrophy diplopia and oscillopsia, and so on as *detailed in* Tables I and II

the present study did not exhibit signs of any neurological involvement either in the brainstem or above it. One of these persons had no neurological signs whatsoever at the time he was seen for our study. His auditory responses were all normal except for the fact that the audiometric configuration for his left ear was arched and he yielded Type II Békésy tracings. The remaining 7 subjects gave evidence of spinal multiple sclerosis. Every one of these persons responded unusually on a few of the auditory tests and the circumstances were such that these responses did not seem to be due to happenstance concomitant peripheral ear pathology. Five of the 7 exhibited decreased sensitivity on the SISI test, 4 obtained abnormally small MLDs, 4 had trouble with speech discrimination in white noise, 3 had arched audiograms, 2 yielded both Type IV Békésy tracings and excess threshold tone decay. 1 had difficulty with the competing speech and filtered speech tests.

The last row in Table VII gives the percentage of noteworthy auditory results obtained from the sample of 7 patients with spinal multiple sclerosis. Although the sample size is small and extensive comment is therefore unjustified, some mention should be made of the mostly normal behavior of these 7 subjects. However, the exceptions to such normality are most interesting. In fact, 1 prominent feature of the group of 7 subjects who had only spinal signs of multiple sclerosis is that auditory behavior was aberrant as often as it was. It seems reasonable to suppose that this behavior was sometimes caused by *higher level neurological lesions which did not manifest themselves during neurological examination.* It should be noted that the auditory profile for 5 of these 7 persons was not particularly dramatic, i.e. auditory dysfunction was subtle and restricted. However, one subject yielded excess threshold tone decay and Type IV Békésy tracings despite normal function on other auditory tests. A second patient showed a number of markedly abnormal auditory findings including excess adaptation and sharply reduced performance on all difficult speech tests. Thus, here is a strong indication that after one has

Table VIII. *Incidence (percentage) of noteworthy auditory results[a] as a function of the number of inferred sites of neurological lesion[b] for 61 patients[c] with multiple sclerosis*

Number of sites of inferred lesion	PTA 25 dB	SRT 25 dB	Speech discrimination 90	Competing speech < 90	Speech in white noise < 60	Filtered speech abnormal	Tone decay < 30 dB	Tone decay > 30 dB	Békésy Type I	Békésy Type II	Békésy Type III	Békésy Type IV	SISI Increased	SISI Decreased	SISI Normal	ABLB EE	ABLB ED	ABLB UR	ABLB UD	ABLB UN	SBMPL EE	SBMPL EU	SBMPL EF	SBMPL UE	SBMPL UU	SBMPL UF	500 Hz MLD < 8 dB	Speech MLD < 6 dB
Two levels or less (N 30)	13	3	3	10	21	16	70	30	21	66	0	14	13	40	37	69	14	14	0	3	70	3	7	17	3	0	33	63
Three or four levels (N 30)	20	13	21	38	48	31	48	52	18	50	4	29	14	61	25	55	24	14	0	7	35	14	10	17	3	0	74	83

[a] The coding in the column headings of the auditory results is done in the same manner as explained in the text and detailed in the footnotes to T ble III. All values are percentage of persons, not ears, possessing the trait of interest.
[b] The levels mentioned are those portrayed in Figure 8 and the explanation thereof. The 7 patients with symptoms of spinal cord damage only are included in the group with 2 sites of inferred lesion or less.
[c] One patient had no neurological symptoms on examination.

Table VII *Incidence (percentage) of noteworthy auditory results*[a] *as a function of the location of inferred sites of neurological lesion*[b] *for 61 patients*[c] *with multiple sclerosis*

Inferred sites of lesion	PTA > 25 dB	SRT > 25 dB	Speech discrimination < 90	Competing speech < 90	Speech in white noise < 60	Filtered speech abnormal	Tone decay < 30 dB	Tone decay > 30 dB	Békésy				SISI			ABLB					SBMPL						500 Hz MLD < 8 dB	Speech MLD < 6 dB
									Type I	Type II	Type III	Type IV	Increased	Decreased	Normal	EE	ED	UR	UD	UN	EE	EU	EF	UE	UU	UF		
Level 4 (N = 8)	25	13	13	0	29	0	88	13	14	86	0	0	38	13	50	63	0	25	0	13	63	0	0	38	0	0	50	80
Levels 3 and 4, 2, 3 and 4 (N = 12)	17	8	17	22	36	0	50	50	25	42	8	25	17	50	33	50	33	8	0	8	50	8	25	8	8	0	56	75
Levels 1 and/or 2, and/or 3 (N = 12)[d]	17	17	9	33	40	50	36	64	18	64	0	18	0	60	40	64	18	18	0	0	64	9	9	18	0	0	50	83
Levels 1–4 (N = 8)	38	13	38	50	63	50	50	50	14	57	0	29	25	63	13	50	25	13	0	13	50	13	13	25	0	0	83	100
Levels 1 and 4, 2 and 4, 1 and 3, 1, 2, and 4, 1, 3 and 4 (N = 14)[d]	7	0	0	14	14	22	71	29	29	50	0	21	7	64	29	77	15	8	0	0	71	14	0	14	0	0	27	64
Spinal cord (S) only (N = 7)	0	0	0	14	29	20	71	29	14	57	0	29	0	71	29	71	14	14	0	0	86	0	0	0	14	0	43	43

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The last row in Table VII gives the percentage of noteworthy auditory results obtained from the sample of 7 patients with spinal multiple sclerosis Although the sample size is small and extensive comment is therefore unjustified some mention should be made of the mostly normal behavior of these 7 subjects However the exceptions to such normality are most interesting In fact, 1 prominent feature of the group of 7 subjects who had only spinal signs of multiple sclerosis is that auditory behavior was aberrant as often as it was It seems reasonable to suppose that this behavior was sometimes caused by higher level neurological lesions which did not manifest themselves during neurological examination It should be noted that the auditory profile for 5 of these 7 persons was not particularly dramatic, i e auditory dysfunction was subtle and restricted However one subject yielded excess threshold tone decay and Type IV Bekesy tracings despite normal function on other auditory tests A second patient showed a number of markedly abnormal auditory findings including excess adaptation and sharply reduced performance on all difficult speech tests Thus, here is a strong indication that after one has

Table VIII *Incidence (percentage) of noteworthy auditory results[a] as a function of the number of inferred sites of neurological lesion[b] for 61 patients[c] with multiple sclerosis*

Number of sites of inferred lesion	PTA 25 dB	SRT 25 dB	Speech discrimination 90	Competing speech 90	Speech in white noise 60	Filtered speech abnormal	Tone decay 30 dB	Tone decay 30 dB	Békésy Type I	Békésy Type II	Békésy Type III	Békésy Type IV	SISI Increased	SISI Decreased	SISI Normal	ABLB EE	ABLB ED	ABLB UR	ABLB UD	ABLB UN	SBMPL EE	SBMPL EU	SBMPL EF	SBMPL UE	SBMPL UU	SBMPL UF	300 Hz MLD 8 dB	Speech MLD <6 dB
Two levels or less (N 30)	13	3	3	10	1	16	70	70	1	66	0	14	13	90	37	69	14	14	0	3	70	3	7	17	3	0	33	63
Three or four levels (N 30)	20	13	1	18	48	31	48	52	18	90	4	79	14	61	25	55	4	14	0	7	55	14	10	17	3	0	74	83

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Table VII *Incidence (percentage) of noteworthy auditory results*[a] *as a function of the location of inferred sites of neurological lesion*[b] *for 61 patients*[c] *with multiple sclerosis*

Inferred sites of lesion	PTA > 25 dB	SRT ≥5 dB	Speech discrimination < 90	Competing speech < 90	Speech in white noise < 60	Filtered speech abnormal	Tone decay ≤ 30 dB	Tone decay > 30 dB	Békésy Type I	Type II	Type III	Type IV	SISI Increased	Decreased	Normal	ABLB EE	ED	UR	UD	UN	SBMPL EE	EU	EF	UE	UU	UF	500 Hz MLD < 8 dB	Speech MLD < 6 dB
Level 4 (N = 8)	25	13	13	0	29	0	88	13	14	86	0	0	38	13	50	63	0	25	0	13	63	0	0	38	0	0	50	80
Levels 3 and 4, 2, 3 and 4 (N = 12)	17	8	17	22	36	0	50	50	25	42	8	25	17	50	33	50	33	8	0	8	50	8	25	8	8	0	56	75
Levels 1 and/or 2, and/or 3 (N = 12)[d]	17	17	9	33	40	50	36	64	18	64	0	18	0	60	40	64	18	18	0	0	64	9	9	18	0	0	50	83
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Levels 1 and 4, 2 and 4, 1 and 3, 1, 2, and 4, 1, 3 and 4 (N = 14)[d]	7	0	0	14	14	22	71	29	79	50	0	21	7	64	29	77	15	8	0	0	71	14	0	14	0	0	27	64
Spinal cord (S) only (N = 7)	0	0	0	14	29	20	71	29	14	57	0	29	0	71	29	71	14	14	0	0	86	0	0	0	14	0	43	43

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Table VIII *Incidence (percentage) of noteworthy auditory results[a] as a function of the number of inferred sites of neurological lesion[b] for 61 patients[c] with multiple sclerosis*

Number of sites of inferred lesion	PTA 25 dB	SRT > 25 dB	Speech discrimination < 90 %	Competing speech < 90	Speech in white noise < 60 %	Filtered speech abnormal	Tone decay 30 dB	Tone decay > 30 dB	Békésy Type I	Békésy Type II	Békésy Type III	Békésy Type IV	SISI Increased	SISI Decreased	SISI Normal	ABLB EE	ABLB ED	ABLB UR	ABLB UD	ABLB UN	SBMPL EE	SBMPL EU	SBMPL EF	SBMPL UE	SBMPL UU	SBMPL UF	500 Hz MLD 8 dB	Speech MLD < 6 dB
T levels or less (N = 30)	13	3	3	10	1	16	70	30	21	66	0	14	13	50	37	69	14	14	0	3	70	3	7	17	3	0	33	63
Three or four levels (N 30)	20	13	21	38	48	31	48	52	18	50	4	79	14	61	25	55	4	14	0	7	55	14	10	17	3	0	74	83

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learned to interpret auditory test findings more adequately in relation to multiple sclerosis such tests may assist importantly in mapping the extent of a patient s sclerotic involvement

Another way of evaluating the relationship between site of neurological lesion and auditory behavior is to divide the 61 subjects on the basis of the number of neurological levels that were inferred to have been affected by sclerotic pathology A breakdown of the findings on this basis is shown in Table VIII Here comparison is made between the 30 subjects with signs attributed only to lesions at 1 or 2 of the levels in Fig. 8 and those with lesions at 3 or 4 of the levels Only the patient with no neurological symptoms at time of examination is omitted from Table VIII Analysis of Table VIII leads to the conclusion stated earlier namely widespread involvement within the CNS is more likely to be associated with auditory dysfunction than is spotty damage Only 30% of the less-involved group had significant threshold tone decay as compared with 52 % of the second group only 21 % of the less-involved subjects could not correctly handle speech in white noise as compared with 48 % of the more-involved group only 33 % of the first group had abnormally small 500 Hz MLDs as compared to 74 % of the second group etc Similar differences in incidence of abnormalities held true for most of the auditory tests

A sub-category of subjects of special interest is that group which exhibited the medial longitudinal fasciculus (MLF) syndrome because this syndrome is indicative of lesions in the midbrain There were 30 such persons The incidence of abnormal behavior for the entire sub-category was as follows 29 could not correctly handle competing message tests, 40 had poor discrimination for monosyllables in white noise 48 had excess threshold tone decay (62 of these bilaterally) 77 yielded Type II or IV Békésy traces (43 of these Type IV) 55 gave decreased SISI scores 26 % demonstrated decruitment 40 had reduced MLDs at 500 Hz, and 72 had reduced MLDs for spondees

One third of these subjects had symptoms attributable to lesions only at the midbrain or higher in the CNS i e., at Levels 1 2, or 3 The remainder also had symptoms suggesting other CNS dysfunction in the low brainstem or cerebellum Although the overall incidence of auditory disorders was somewhat greater in the group with widespread lesion as would be expected those with only high CNS damage also performed poorly on many auditory tests 50 had excess threshold tone decay 75 gave Type II or IV Békésy traces, 63 achieved low SISI scores, and 33 % had reduced MLDs for 500 Hz.

The important conclusions to be drawn from the foregoing discussion are that first this population as far as could be determined from detailed neurological data, was one characterized by lesions throughout the central nervous system and that second a significant proportion of the abnormal auditory behavior must be considered symptomatic of lesions central to the first order auditory neurons and their termini In other words, as is clear from the above discussion, clinically inferred lesions in the upper brainstem, midbrain and cortical areas of the CNS are as likely and in certain cases more likely to be paired with unusual auditory behavior than are those confined to the general area of the low brainstem Consequently it seems only reasonable to conclude that these aberrations in auditory behavior can be ascribed to multiple sclerotic lesions in the central auditory nervous system and that many of them are results of damage located central to the root of the VIIIth cranial nerve

III VESTIBULAR RESULTS IN RELATION TO NEUROLOGICAL FINDINGS

Forty four of the subjects in this study were given the formalized electronystagmographic examination described in Chapter II The distributions (percentages) of vestibular symptoms which emerged were classified in terms of the locations of the inferred sites of neurological lesion in Table IX and on the basis of the number of inferred sites in Table X

Table IX. *Incidence (percentage) of abnormal vestibular results*[a] *as a function of the location of inferred sites of neurological lesion*[b] *for 44 patients*[c] *with multiple sclerosis*

Inferred sites of lesion	Abnormal optokinetic tracking (A)	Abnormal pendulum tracking (B)	Positional nystagmus (C)	(Post-caloric) hyperexcitability (D)	Poor or reversed attenuation (E)	Unilateral paresis (F)	Abnormal slow tracking (G)	Dysrhythmia (H)	Spontaneous nystagmus (I)	Directional preponderance (J)	Lateral gaze imbalance (K)
Level 4 (N = 6)	33	33	33	83	50	83	17	50	17	33	17
Levels 3 and 4, 2, 3, and 4 (N = 9)	56	56	22	33	56	33	33	44	22	56	0
Levels 1 and/or 2, and/or 3 (N = 7)[d]	71	57	71	29	43	57	29	43	43	14	14
Levels 1–4 (N = 6)	67	67	17	50	50	50	100	33	33	50	33
Levels 1 and 4, 2 and 4, 1 and 3, 1–4, and 4, 1–3, and 4 (N = 11)[e]	73	64	36	64	55	9	45	55	55	36	27
Spinal cord (S) only (N = 5)	40	20	100	60	20	0	0	20	60	20	20

[a] The coding in the column headings of the vestibular results is done in the same manner as explained in the text. See Table VI and the footnotes for Table III.
[b] The levels mentioned are those portrayed in Fig. 8 and the explanation thereof. The last row contains values obtained from those patients with symptoms of spinal cord damage only at the time of neurological evaluation.
[c] One patient had no neurological signs on examination.
[d] One patient is common to these 2 groups.

Even though the number of subjects in each category of Table IX is small, the following general trends may be observed therein. The 6 individuals with involvement limited to Level 4 (brainstem) showed high incidences of post-caloric hyperexcitability (83 %), unilateral paresis (83 %) and dysrhythmia (50 %). The 9 subjects having brainstem symptoms (Area 4) plus midbrain involvements (Level 3 or Levels 2 and 3) had approximately 50 % incidence of all symptoms except positional nystagmus (22 %), abnormal slow tracking (33 %), post-caloric hyperexcitability (33 %), unilateral paresis (33 %), spontaneous nystagmus (22 %), and lateral gaze imbalance (0 %). A high proportion of the 7 persons showing cortico-optic (Level 1) plus midbrain (Levels 2 or 3) neurological symptomatology exhibited abnormal optokinetic tracking (71 %) and positional nystagmus (71 %), with few showing lateral gaze imbalance, directional preponderance, abnormal slow tracking, or hyperexcitability. Other vestibular symptomatology (see Table IX) was noted in about half the subjects. The 6 persons with inferred lesions in all 4 areas exhibited abnormal slow tracking, two-thirds of them yielded abnormal optokinetic tracking and abnormal pendulum tracking; half showed hyperexcitability, poor attenuation, unilateral paresis, and directional preponderance while a third or less showed unsolicited nystagmus, lateral gaze imbalance, or dysrhythmia. Another group of subjects (*11*), with apparently spotty neurological involvement, had a high percentage of abnormal optokinetic tracking (73 %), *abnormal pendulum tracking* (64 %), and post-caloric hyperexcitability (64 %) combined with very infrequent unilateral paresis (9 %).

The 5 persons whose only inferred lesions were in the spinal cord yielded little evidence of vestibular dysfunction. Notice in Table IX that incidence was 20 % or less in 7 of the 11 cate-

learned to interpret auditory test findings more adequately in relation to multiple sclerosis, such tests may assist importantly in mapping the extent of a patient's sclerotic involvement

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A sub-category of subjects of special interest is that group which exhibited the medial longitudinal fasciculus (MLF) syndrome because this syndrome is indicative of lesions in the midbrain There were 30 such persons The incidence of *abnormal behavior for the entire sub-category* was as follows 29 could not correctly handle competing message tests 40 had poor discrimination for monosyllables in white noise 48 had excess threshold tone decay (62 of these bilaterally) 77 yielded Type II or IV Békésy traces (43 of these Type IV), 55 gave decreased SISI scores 26 demonstrated decruitment, 40 had reduced MLDs at 500 Hz, and 72 had reduced MLDs for spondees

One third of these subjects had symptoms attributable to *lesions only at the midbrain or* higher in the CNS i e., at Levels 1 2, or 3 The remainder also had symptoms suggesting other CNS dysfunction in the low brainstem or cerebellum. Although the overall *incidence of auditory* disorders was somewhat greater in the group with widespread lesion as would be expected those with only high CNS damage also performed poorly on many auditory tests 50 had excess threshold tone decay 75 gave Type II or IV Békésy traces, 63 achieved low SISI scores, and 33 % had reduced MLDs for 500 Hz.

The important conclusions to be drawn from the foregoing discussion are that first this population as far as could be determined from detailed neurological data was one characterized by lesions throughout the central nervous system and that second a significant proportion of the abnormal auditory behavior must be considered symptomatic of lesions central to the first order auditory neurons and their termini In other words, as is clear from the above discussion, clinically inferred lesions in the upper brainstem, midbrain, and cortical areas of the CNS are as likely and in certain cases more likely to be paired with unusual auditory behavior than are those confined to the general area of the low brainstem Consequently it seems only reasonable to conclude that these aberrations in auditory behavior can be ascribed to multiple sclerotic lesions in the central auditory nervous system, and that many of them are results of damage located central to the root of the VIIIth cranial nerve

III VESTIBULAR RESULTS IN RELATION TO NEUROLOGICAL FINDINGS

Forty-four of the subjects in this study were given the formalized electronystagmographic examination described in Chapter II The distributions (percentages) of vestibular symptoms which emerged were classified in terms of the locations of the inferred sites of neurological lesion in Table IX and on the basis of the number of inferred sites in Table X

there are particular relationships of interest to the reader which are not discussed in the text, he will find references to Tables IV V VII, and VIII useful.

A. Threshold sensitivity for pure tones

The pure tone threshold levels exhibited by the 61 subjects were sufficiently good to allow the conclusion that substantial hearing loss was not a hallmark of the group. Neither however can the results be classified as free from unusual characteristics Depression in sensitivity at 1 or more frequencies ranged from mild (30 or 35 dB HL) to severe (over 65 dB HL) in 64 of the 122 ears involved. This means that in only 58 instances was sensitivity 25 dB HL or better across the entire frequency range. These proportions are not typical, particularly when one recalls that poor thresholds often occurred at unusual frequencies. Consider also the audiometric patterns that the group exhibited. It is particularly noteworthy that the arched pattern, uncommon in the hearing impaired population, except possibly in the very elderly population (Goetzinger et al 1961), appeared 17 times The 61 multiple sclerotic patients studied here were not an elderly group Also predominantly low frequency deficits as compared to those in the mid-frequencies appeared 8 additional times in other audiometric contours Furthermore recall that in the group of ears with normal thresholds, 11 had arched contours and 7 had rising configurations. Thus, one comes to the conclusion that many of our 61 subjects exhibited subtle but real disturbances in sensitivity for pure tones in consequence of their multiple sclerosis and that one of the most distinctive (but not necessarily the most important) symptoms of such disturbance was the arched audiometric pattern

It is intriguing to speculate on the significance of the arched contour This pattern is characterized by better hearing in the mid-frequencies, (often within the range of normal sensitivity) than in the low or high frequencies. Given the apparent orderliness of the auditory system tonotopically such a configuration is difficult to envision as resulting from a localized and specific invasion of the VIIIth nerve trunk or of some deeper portion of this tonotopic system. Granted, such a geographically unique invasion might occur rarely but its repeated appearance would require an astonishing geographic predilection for the sclerotic invasion to occupy uniquely restricted areas. This possibility is most unlikely A more reasonable explanation would seem to be that a variety of lesions beyond the VIIIth nerve trunk disrupt to some degree the mechanisms involved in transmitting frequency information within the central nervous system. One can at present only guess at what these mechanisms are but they must exist. It is unlikely that the auditory nervous system furnishes only a series of replicative transmission paths through the various levels from cochlea to cortex. Moreover at least peripherally the volley mechanism probably is predominant at low frequencies, with the place mechanism increasing its predominance as frequency increases. Such a dual system must depend upon dissimilar central response to incoming volley and to incoming place information, with the consequent prospect that central lesions affecting transmissional pathways and neuronal networks may disrupt perception of some frequencies more than others. Among other things, it is reasonable to presume that such disruptions could include both efferent and afferent functions, as well as the interactions between them [1] In point of fact, 1 in every 3

[1] Gravendeel (1958), although not specifically discussing multiple sclerosis, postulates mechanism which, if present, could account for the low frequency deficit in the arched audiogram. He presumes that low frequency hearing loss can be caused by hyperactivity of the efferent system He suggests that lesions within the central auditory system can produce such hyperactivity He reports obtaining the arched configuration from patients with disease processes and/or surgical intervention in the fourth ventricle, the mesencephalon and the lateral lemniscus It is Gravendeel's contention that the low frequency component of hearing loss in these cases was due to a resultant hyperactive efferent system and that the high frequency component, which was occasionally transitory was due to dysfunction of the afferent fibers in the brainstem and/or higher CNS Along this line it is of interest that slight low frequency hearing deficits have been reported for poliomyelitis (Button & McConnell, 1958 McConnell & Button, 1962) Other authors have proposed that low

Table X *Incidence (percentage) of abnormal vestibular results[a] as a function of the number of inferred sites of neurological lesion[b] for 44 patients[c] with multiple sclerosis*

Number of inferred sites of lesion	Abnormal optokinetic tracking (A)	Abnormal pendulum tracking (B)	Positional nystagmus (C)	(Post-caloric) hyperexcitability (D)	Poor or reversed attenuation (E)	Unilateral paresis (F)	Abnormal slow tracking (G)	Dysrhythmia (H)	Spontaneous nystagmus (I)	Directional preponderance (J)	Lateral gaze imbalance (K)
Two levels or less ($N=22$)	43	45	59	64	45	27	18	45	50	77	18
Three or four levels ($N=21$)	71	62	4	38	43	43	62	38	24	48	19

[a] The coding in the column headings of the vestibular results is done in the same manner as explained in the text. See Table VI and the footnotes for Table III

[b] The levels mentioned are those portrayed in Fig. 8 and explanation thereof The 5 patients with symptoms of spinal cord damage only are included in the group with 2 sites of inferred lesion or less.

[c] One patient had no neurological symptoms on examination.

gories of vestibular abnormality The prominent exceptions to such behavior were the 3 persons who exhibited post-caloric hyperexcitability the 3 who possessed spontaneous nystagmus, and the 5 persons (the entire group) who had positional nystagmus Since only 5 subjects with spinal multiple sclerosis were given the vestibular evaluation it is difficult to determine whether the abnormalities detected were results of CNS lesion not discovered on neurological evaluation of concomitant pathology or simply of chance occurrences However it does not seem highly probable that the observation of positional nystagmus in all 5 subjects with only spinal symptoms could be chance alone

When the data are considered in terms of the number of areas affected (Table X) positional nystagmus, post-caloric hyperexcitability and spontaneous nystagmus were more prevalent in the group (N = 22) having involvement at 1 or 2 levels than in the group (N = 21) with 3 or 4 levels affected The reverse was true for abnormal optokinetic tracking, abnormal pendulum tracking, unilateral paresis and abnormal slow tracking. The 2 groups were essentially equivalent in terms of the remaining vestibular symptoms.

It is clear from these results that abnormalities revealed by the ENG evaluation were not confined to those subjects with symptoms referrable to lesions in Level 4 the area within which the vestibular branch of the VIIIth nerve terminates in the vestibular nuclei Conversely except for abnormal slow tracking in the 6 cases where all 4 areas were involved and the 5 spinal cord subjects with positional nystagmus no vestibular symptom was always associated with a particular configuration of inferred neurological lesion As with the auditory results, this outcome is not startling in view of the diversity of pathology suffered by multiple sclerotic patients Finally and this generalization is not apparent from the tables that are given the ENG results did not appear to correlate with the auditory results in a meaningful manner This latter outcome may be the result of the limited sample of data currently available Hopefully further research will clarify this situation

IV IMPLICATIONS OF SPECIFIC AUDITORY FINDINGS

The ensuing discussion concerns itself with how the results of the various auditory tests administered to these subjects can be interpreted in terms of the causes of abnormality and what the implications of such analysis may be If

competing message test is produced primarily by temporal lobe dysfunction and multiple sclerosis has a predilection for sites lower within the CNS therefore high level auditory symptoms would not be expected too often.

Aberrant behavior appeared more commonly when discrimination was measured against a background of white noise, falling below 60% for 28 of the ears through which the test was administered. Moreover discrimination in quiet was also reduced in only 8 of these 28 instances. The remaining 20 cases represent instances in which breakdown was not revealed by any of the traditional measures already discussed. When one takes into account the concomitant results for the several tonal tests discussed earlier it would appear that these results bespeak in most cases brainstem lesions that did not produce noteworthy loss in either hearing sensitivity or speech discrimination in quiet. Of course, there are the cases alluded to before in which difficult speech tests demonstrated breakdown in the absence of abnormality on tonal tests, and it is reasonable to assume that these findings result from higher level CNS damage. Of particular interest is the fact that reduced performance on competing message tasks usually heralded similar or greater difficulty on the speech in white noise test. Sinha (1959) has suggested that temporal lobe disease can affect the understanding of speech presented against a background of white noise. The opposite of this situation is not invariably true, i.e. breakdown on speech in white noise tasks does not invariably presage trouble when competing messages are presented to the ears. The obvious conclusion is that the speech in white noise test is sensitive to the presence of damage in more parts of the auditory system than is the competing message test. This conclusion is supported by the fact that although breakdown in discrimination for speech in white noise was most common in those subjects with neurologically placed lesions at Levels 1–4 (63% abnormal), it was also common in persons whose lesions were thought to be limited to regions superior to Level 4 (40% abnormal). As with most tests, the more widespread the symptoms of CNS lesion, the higher the incidence of abnormality.

Breakdown on the filtered speech test occurred 9 times out of 72 presentations, and then predominantly when discrimination in quiet was excellent. Only half the time was filtered speech reception abnormal when competing speech scores were low but speech in white noise scores were usually abnormal if filtered speech produced difficulty. This difficulty was almost always unilateral, i.e., if scores were reduced, the decrease in performance was almost always monaural. In addition aberrations for filtered speech tended to cluster in relation to the results on the other tests in such a manner that, in the authors' opinion this test as presented here almost exclusively revealed breakdown via 1 ear that is, it almost never provided information suggesting damage to binaural correlative mechanisms. Finally breakdown on this test, when it did occur was much more common in persons whose lesions were inferred to be in Levels 1–3 than at Level 4. Thus, the filtered speech test used in this study probably was much more sensitive to high level CNS lesions than to low level ones. If some of the patients possessed lesions of the binaural correlative mechanisms within the CNS, this test did not emerge as sensitive to such lesions.

D. Threshold tone decay

The traditional interpretation of threshold tone decay is that excess amounts of decay (more than 30 dB) are indicative of retrocochlear involvement. This degree of abnormality was apparent via 38 of the 120 ears tested for such behavior. This proportion is much higher than would appear in an ordinary population with hearing as good as the 61 subjects discussed here (Willeford, 1960). Hence, one may conclude that in most of the instances where excess tone decay appeared, the test was revealing an aberration of function brought about by sclerotic lesions.

The distribution of results gives some clue to the probable loci of lesions. Of the 38 ears with threshold tone decay exceeding 30 dB, 23

persons exhibiting the arched pattern had neurological signs suggesting midbrain or higher CNS lesions. Almost all of these had bilateral arched configurations and also yielded abnormal responses on most tests of special interest was the fact that 67 % had excess tone decay 33 % bilaterally

Remembering that central auditory lesions usually have little influence on pure tone thresholds, one may reason that the cases among these subjects in whom the symptoms just discussed were *present probably* possessed appreciable involvement within the auditory CNS Furthermore the fact that aberrations such as the arched contour were monaural in many instances may be taken as evidence confirming the view that for a substantial distance the CNS maintains 2 functionally independent (although closely interconnected) *auditory* pathways, each serving 1 ear Finally since pure tone sensitivity is relatively unaffected by central lesions and pathologies (Bunch, 1928 Bocca & Calearo 1963 Stein, 1963 Jerger 1964) unless the involvement is bilateral and extensive (Jerger 1970) the fact that a patient did not show elevated thresholds *to pure tones does not rule out the* possibility that he possessed central auditory pathology that manifested itself in unusual threshold configurations and/or in other ways when faced with more difficult auditory tasks.

B Threshold sensitivity for speech

Speech reception thresholds were poorer than 25 dB for only 6 ears. Tests of these same ears yielded pure tone averages for 500–2 000 Hz of similar severity This proportion of loss is slightly higher than a random selection of adults in the same age range would be expected to yield However the overall pattern of findings suggests that peripheral hearing loss was probably present for half these ears Consequently since (CNS) lesions were clearly present in the subjects under study the lack of widespread insensitivity for spondee materials suggests that responsiveness to this type of speech can remain *adequate despite appreciable* involvement of the auditory pathways and centers. Of course it would not be surprising to find specific instances in which the situation is different.

C. Discrimination for speech

Perception of monosyllables in quiet surroundings was for the most part very good. For only 9 ears (7 individuals) was the discrimination score poorer than 90 %. In 4 of these cases, an appreciable hearing loss was apparent for 500–2 000 Hz pure tones and in 3 of them, a loss was present for spondees. Since all cases of reduced discrimination for speech in quiet were not thus accounted for it was concluded that reduced discrimination occasionally indicated a breakdown in function that was not already revealed by sensitivity measurements Six of the 7 individuals involved had neurological symptoms thought attributable to Level 4 and 3 of these *6 had lesions at all 4 levels. Thus, breakdown of* accurate speech discrimination was usually accompanied by damage in the region of the auditory nuclei and trapezoid body and/or was widespread in the CNS However there are other individuals in the sample with similar loci of inferred lesion whose discrimination was good

The situation proved to be slightly different for the competing speech test Twelve individuals obtained lower than normal scores on this test Five of these persons also yielded reduced scores in quiet for 1 or both ears *Interestingly in only* 1 ear among those ears (7) through which reduced discrimination scores in quiet were obtained was the score on the competing message task dramatically reduced re the score in quiet Of the other 8 ears, however 6 had impaired performance for competing speech through 1 ear and 1 case via both ears even though discrimination in quiet via *both ears was excellent The* relatively few instances of breakdown on this test are understandable since difficulty on the

frequency hearing losses in multiple sclerosis are due to lesions manifesting themselves as conductive hearing loss (Simpkins, 1961) or due to damage to the VIIIth nerve (Sopek & Sipowicz, 1969) These possibilities do not seem to us as likely

hroughout the 3 minutes that were allotted to a ingle tracing. Thus, it may well be that the damage inflicted on central auditory structures by demyelination often shows itself as modest, ongoing adaptation of threshold responsiveness to continuous tones. If so, the resultant tracings were classified as Type II because the total extent of this adaptation did not exceed the shift re the interrupted tracing (20 dB) specified as the maximum for a Type II result.

In this regard, it is pertinent to note that there were 17 instances of Type IV tracings, but that these, too, were usually characterized by a continuing slow drift. Such Type IV tracings were analogous, except for their more rapid drift, to the Type II tracings mentioned above. Hence, it may well be artificial in the present instance to make a distinction between Type II and Type IV results. Both sets probably represent similar symptomatology differing in degree rather than kind. From this point of view both may be attributed to disruption of central processes. Moreover the critical feature is that both are clearly unlike the rapid, disruptive adaptation so often caused by VIIIth nerve lesions which reveals itself in the Type III Békésy tracing.

The most startling fact in the Békésy data is that Type III tracings emerged only 2 times out of 115 series of tests and these 2 examples of extreme adaptation were obtained via the 2 ears of 1 subject. This subject also had extreme, bilateral, threshold tone decay. The rarity of this symptomatology in the present series of subjects is unexpected, but it supports the previously expressed view that serious involvement of the VIIIth nerve trunk probably was not a frequent manifestation of multiple sclerosis in this population.

The relationships observed between the Békésy tracings and excess tone decay warrant further comment. Thirteen of the 14 persons with severe bilateral tone decay were also given Békésy tests. Considered by ears, there were 11 Type IV, 10 Type II, 3 Type I and 2 Type III tracings. One sees here a combination of results which is clinically unique, namely a consistent linkage of excess tone decay and either Type IV or Type II Békésy traces. This relation appears to be another clue that the excess adaptation exhibited by many patients with bilateral tone decay was due to lesions deep to the auditory nerve trunks. A further point of interest is that 15 of the 17 instances of Type IV tracing involved ears through which excess tone decay was also recorded. This is one of the few circumstances within the findings in which nearly all aberrant responses on 1 test were matched by aberrant responses on another. Clearly therefore, the Type IV tracings encountered here seemed to depend on a disruption of central function which also manifested itself through excess tonal adaptation.

F Short increment sensitivity

High SISI scores were obtained via 14 ears when the test was administered at 20 dB SL. These responses were found predominantly in cases with some impairment in pure tone sensitivity, Type II Békésy tracings, and modest tone decay. In view of this combination of symptoms, it is likely that at least for the most part, these high SISI scores were indications of occasional end-organ involvement that was not related to the patient's multiple sclerosis. There were a few cases where high SISI scores appeared in combination with conventional retrocochlear findings, but the sample size here is so small that speculation about this circumstance is unwarranted.

Conversely there were 52 instances where short increment sensitivity was substantially poorer than normal. These were subjects who either could not detect 2.5 dB increments at 20 dB SL and/or at 85 dB HL or else who scored 55% or less at 85 dB HL for at least 1 test frequency. This concentration of atypical responses is very high and probably should be interpreted as resulting from multiple sclerosis. Curiously the incidence of decreased SISI scores clusters around 50–60 in almost any group of subjects chosen on the basis of their neurological symptoms. This finding suggests that extensive CNS lesions affecting the auditory system, regardless of the level at which they occur can produce the

had normal threshold sensitivity at the frequency where maximum decay was elicited and none of the other 15 had loss greater than 40 dB at these frequencies Moreover 31 of the 38 ears in question did not exhibit a deficit exceeding 35 dB at any frequency The lack of reduced threshold sensitivity for these 38 ears is unlike the typical finding with cases of VIIIth nerve tumor where excess tone decay is accompanied by definite hearing loss [1] One is therefore led to the opinion that in the instances under consideration, the excess tone decay was caused by lesions more centrally located than the VIIIth nerve trunk.

This view is supported by the fact that 14 of the 61 subjects had bilateral threshold tone decay and there were only 10 instances of unilateral threshold tone decay The probability of both VIIIth nerve trunks being affected in 1 out of every 4 of the subjects in this sample or of at least 1 VIIIth nerve trunk being affected in 2 out of every 5 is unlikely Even more telling is the fact that although 12 of these individuals (20 ears) had complete threshold tone decay at some frequency 8 of them bilaterally they had good hearing in other respects These cases did not show the gross symptoms of breakdown that usually accompany malfunction of the auditory nerve It should be especially noted that their discrimination for speech in quiet was excellent 34 of the 38 ears via which extreme threshold adaptation was elicited had speech discrimination scores of 90 or better Remember that in patients with VIIIth nerve tumor sharply impaired discrimination for speech in quiet is a common symptom

Although the case for claiming that the excess tone decay encountered in this study is due to lesions above the VIIIth nerve is especially strong for the subjects with bilateral decay the same conclusion emerges from the data on unilateral tone decay Here, too the concomitant findings were good hearing for pure tones and for speech Interestingly the cases exhibiting unilateral decay showed less severe adaptation than those with bilateral decay only 3 of 10 unilaterals had complete tone decay but 9 of 14 bilaterals had complete tone decay 8 of them bilaterally In addition, the unilateral cases usually had Type I or II Békésy traces (7 of 10) while half the bilateral cases (13 of 26) had Type III or IV traces. Possible implications of these last findings are that different loci of sclerotic lesion are indicated by these two patterns of response and that the cases of bilateral decay may often result from manifestations of more widespread CNS lesion.

Another facet of the threshold performance of these subjects is that their threshold configurations were quite atypical of VIIIth nerve lesion e.g., 25 of the 38 had flat, arched, rising, or notched configurations.

E. Békésy threshold tracing

Békésy threshold tracings were obtained via 115 ears. Thirty-four of the result were Type I tracings, while 62 were Type II Type III tracings occurred only twice and 17 were Type IV In view of the fact that the population in question is characterized by CNS lesions, this distribution of findings is most provocative One point of interest is the relatively small proportion of patients who yielded exclusively Type I records A full 70 % of the tracings were abnormal in some way One must assume that the majority of these abnormal tracings were manifestations of multiple sclerosis, since a proportion of this magnitude is in no way typical of the population at large Equally provocative is the fact that more than 50 of all sets of tests yielded some Type II tracings This fraction too is out of line with the population at large Moreover Type II tracings are traditionally interpreted to indicate cochlear lesions, and the group of subjects being discussed here is one in which cochlear lesions were rare at most and CNS involvement was the rule The most reasonable interpretation of this paradox would seem to be that Type II tracings can result from central auditory lesions, but that this situation has gone unnoticed because patients with such lesions are in the minority in ordinary clinical situations Here incidentally it is pertinent to remind the reader that many of the Type II records in question were unusual in that they revealed slow ongoing adaptation

nce. As a final comment, it is interesting to observe that this imbalance usually was not concomitant with the type of breakdown in processing of binaural information revealed by the filtered speech test.

I. Masking level differences

Twenty-three of the 47 persons so tested had MLDs at 500 Hz that were abnormally small (7 dB or less) and the same was true of 30 out the 42 persons given the test with spondees (5 dB or less). Thus, unusual MLD performance was very common. Particularly noteworthy in this regard is the fact that almost all of the persons yielding small MLDs had bilaterally normal thresholds for 500 Hz and for spondees. For this reason, it seems safe to assume that 2 potential sources of decreased release from masking, namely end-organ pathology and VIIIth nerve damage, were absent in a preponderance of these subjects. This interpretation leads to the further assumption that the reduced MLDs exhibited by this population were the result of lesions within the central nervous system.

One might presume that the proper functioning of cross-correlational mechanisms at the medullo-pontine level are particularly critical in achieving normal MLDs, e.g. that the initial separation of signal from background occurs in the centers where binaural stimuli are first mixed. However, when one considers the results in relation to the inferred sites of neurological lesion in our population, one finds that the incidence of reduced MLDs was as great in those cases where the brainstem was not involved as in those cases where only the brainstem was involved or where the midbrain was affected along with the brainstem. Thus, it would appear that MLD performance is sensitive to pathology throughout much of the central auditory nervous system. Moreover, the fact that MLD tests yielded such a high proportion of abnormal responses suggests that these tests are quite sensitive to the lesions which multiple sclerosis produces. Spondee materials appear to be particularly good in this regard.

One must remember that normal release from masking (large MLDs) can occur only if cross-correlational mechanisms are interrelating binaural stimulus trains properly. As already mentioned, it appears from the present findings that the critical cross-correlational processes are not limited to the brainstem. One may speculate that a possible source of disruption in cross-correlational function may be a change in neural transmission (McDonald & Sears, 1970) engendered by partial or complete demyelination within the auditory tracts which disrupts the synchrony and completeness of the nerve impulse trains reaching correlational centers at more than 1 level in the central auditory nervous system.

V. FINAL COMMENT

The foregoing discussion is incomplete. There is still a tremendous amount to be learned about the auditory responses of multiple sclerotic patients, about the change in these responses over time, and about the relationship of these responses to the lesions that produce them. Therefore, the remarks in this chapter must be considered merely as early thoughts in the search for this knowledge. Nonetheless, 2 features of the data stand out as deserving mention.

First, the great majority of these multiple sclerotic patients in this sample exhibited aberrant auditory behavior. These manifestations of auditory abnormality were usually subtle. Such tests as those determining sensitivity for pure tones or spondaic words or those probing speech discrimination in quiet settings were generally performed in a normal or only slightly depressed fashion by this group. However, more difficult speech and tonal tests often revealed unusual auditory behavior. The information at hand does not yet allow one to draw generalizations indicating the interpretative significance of clusterings of audiological findings. However, interrelations exist and further study of the auditory behavior of multiple sclerotic patients coupled with good neurological data (and post mortem findings when available) should lead to such generalizations. If they do so, the use of

abnormal SISI scores It is noteworthy however that a substantial fraction of such responses occurred for ears evidencing excess tone decay and/or Type II or Type IV Békésy tracings. Thus one may speculate that the same central lesions which produced the latter types of response often brought about desensitization to short increments of intensity

G Loudness balance

Twenty two of the 59 subjects who were given the ABLB test evidenced atypical loudness relations In 8 instances, recruitment was present and here there was also a tendency for tone decay to be modest, Békésy tracings to be Type II and SISI scores to be high. Thus, some of the recruitment responses observed here are probably attributable to conditions other than multiple sclerosis. In some ears, though recruitment was elicited in combination with otherwise predominantly retrocochlear signs There is, as yet an insufficient group of subjects of this sort to make comment meaningful

The remaining 14 persons with abnormal ABLB responses exhibited decruitment or no recruitment in ears with hearing loss Excess tone decay Type IV Békésy tracings, and desensitization to short increments of intensity appeared in over half of these ears. Such clustering leads to the speculation that these several symptoms may have been due to the same sclerotic lesions. If so and since it is reasonable to presume from neurological evaluation of these subjects and from other auditory signs that many of the lesions were in the brainstem and mid brain decruitment would also at times be the product of such involvement Such a situation would not preclude its appearing in other individuals because of cortical lesions (Davis & Goodman 1966) or VIIIth nerve damage (Tillman 1969)

H Median plane localization

Forty-eight subjects required equally intense tones in the 2 ears to achieve a median plane localization and 12 others either could not experience a midline image or else did so only when unequal stimulation was present at the 2 ears. The latter 12 individuals may be judged to have shown aberrant responses in the sense that both normal hearers and sensorineural loss cases usually achieve localization with approximately equal intensities at the 2 ears. Such aberrance has been found in consequence of VIIIth nerve damage but also occurs when the damage is deeper (Jerger 1960*b*) It is interesting to observe that among the present group of subjects, abnormal localization occurred only 3 times in conjunction with decruitment but it appeared 9 times in instances where large SISI increments were not heard 5 times when there was excess tone decay and 8 times when MLDs were abnormally small These relations lead to the speculation that this aberrance in response to the localizational task is indicative of lesions that are dissimilar to those inducing decruitment. However this is a prospect that can be clarified only through substantial future exploration.

An outstanding feature of the present findings is that of the 12 multiple sclerotic subjects yielding abnormal median plane localization results, only 5 had difficulties in performing the localization task Thus, only a twelfth of the cases with multiple sclerosis suffered from this problem It has long been known that patients with brainstem lesions often find this task tremendously taxing in that they have great difficulty either perceiving a localizable image or in getting this image to shift Since neurological results suggest that brainstem lesions were common in this group the limited incidence of gross breakdown in lateralizational ability can be interpreted as indicating that multiple sclerosis often did not produce lesions which totally disrupted intracranial localizational ability although in some cases its lesions appeared to cause the more subtle imbalance in the central processing of interaural signals that necessitates use of interaural intensity differences to achieve a centered image However in some cases the damage was of such nature as to disrupt the mechanism underlying the lateralization experi-

ence As a final comment, it is interesting to observe that this imbalance usually was not concomitant with the type of breakdown in processing of binaural information revealed by the filtered speech test.

I. Masking level differences

Twenty-three of the 47 persons so tested had MLDs at 500 Hz that were abnormally small (7 dB or less) and the same was true of 30 out the 42 persons given the test with spondees (5 dB or less) Thus, unusual MLD performance was very common. Particularly noteworthy in this regard is the fact that almost all of the persons yielding small MLDs had bilaterally normal thresholds for 500 Hz and for spondees. For this reason, it seems safe to assume that 2 potential sources of decreased release from masking, namely end-organ pathology and VIIIth nerve damage, were absent in a preponderance of these subjects This interpretation leads to the further assumption that the reduced MLDs exhibited by this population were the result of lesions within the central nervous system

One might presume that the proper functioning of cross-correlational mechanisms at the medullo-pontine level are particularly critical in achieving normal MLDs, e g that the initial separation of signal from background occurs in the centers where binaural stimuli are first mixed. However when one considers the results in relation to the inferred sites of neurological lesion in our population, one finds that the incidence of reduced MLDs was as great in those cases where the brainstem was not involved as in those cases where only the brainstem was involved or where the midbrain was affected along with the brainstem Thus, it would appear that MLD performance is sensitive to pathology throughout much of the central auditory nervous system Moreover the fact that MLD tests yielded such a high proportion of bnormal responses suggests that these tests are quite sensitive to the lesions which multiple sclerosis produces. Spondee materials appear to be particularly good in this regard

One must remember that normal release from masking (large MLDs) can occur only if cross-correlational mechanisms are interrelating binaural stimulus trains properly As already mentioned, it appears from the present findings that the critical cross-correlational processes are not limited to the brainstem. One may speculate that a possible source of disruption in cross-correlational function may be a change in neural transmission (McDonald & Sears, 1970) engendered by partial or complete demyelination within the auditory tracts which disrupts the synchrony and completeness of the nerve impulse trains reaching correlational centers at more than 1 level in the central auditory nervous system.

V FINAL COMMENT

The foregoing discussion is incomplete. There is still a tremendous amount to be learned about the auditory responses of multiple sclerotic patients, about the change in these responses over time, and about the relationship of these responses to the lesions that produce them. Therefore, the remarks in this chapter must be considered merely as early thoughts in the search for this knowledge. Nonetheless, 2 features of the data stand out as deserving mention

First, the great majority of these multiple sclerotic patients in this sample exhibited aberrant auditory behavior These manifestations of auditory abnormality were usually subtle Such tests as those determining sensitivity for pure tones or spondaic words or those probing speech discrimination in quiet settings were generally performed in a normal or only slightly depressed fashion by this group. However more difficult speech and tonal tests often revealed unusual auditory behavior The information at hand does not yet allow one to draw generalizations indicating the interpretative significance of clusterings of audiological findings. However interrelations exist and further study of the auditory behavior of multiple sclerotic patients coupled with good neurological data (and post mortem findings when available) should lead to such generalizations. If they do so the use of

audiological procedures will eventually come to have unique value in assisting in the identification of sclerotic pathology in the living person

Second, remember that involvement of the VIIIth nerve trunk appeared to be relatively rare in the group of patients with multiple sclerosis under study Most of the distinctive auditory symptomatology these individuals exhibited is consequently attributable to disturbances within the central auditory nervous system Much of this symptomatology mimicked responses traditionally associated with inner ear lesions although some mimicked behavior induced by VIIIth nerve pathology Clearly it becomes necessary to rethink the diagnostic significance of the entire array of auditory tests when CNS lesions such as multiple sclerosis are a possibility This does not mean that test findings do not have the conventional meanings when encountered in the presence of peripheral auditory diseases and disorders It does mean that the same findings can have new meanings when CNS lesions are present. Here, too is an area where the further study of the auditory behavior of multiple sclerotic subjects coupled with good supporting data should prove most productive.

Zusammenfassung

Dieser Anhang präsentiert auditorische vestibuläre und neurologische Daten, die von 61 Personen stammen, die an multipler Sklerose erkrankt sind. Diese Menschen wurden weitgehenden Testen auf den oben genannten Gebieten ausgesetzt, um dadurch mehr über die Funktion des menschlichen zentralen auditorischen und vestibulären Nervensystems zu lernen. Auditorische und vestibuläre Erkenntnisse wurden im verhältnis zur neurologischen Mitwirkung des unteren Hirnstammes, des oberen Hirnstammes, des Mittelhirns und der Rinde analysiert, wie die neurologischen Untersuchungen ergaben. Die Folgerungen, die man aus den Testergebnissen ziehen konnte, wurden mit den Tatsachen vor Augen, dass multiple Sklerose eine Krankheit des zentralen Nervensystems ist, beachtet.

Die neurologischen Bewertungen enthielten Untersuchungen des Krankheitswerdegangs, der klinischen, laboratorischen und medizinischen Berichte die von allen Kranken zur Verfügung stand und genaue klinische, neurologische von dem Neurologen unseres Projektes unternommene Untersuchungen. Mit Hilfe solcher und, wenn nötig, anderer besonderer Methoden, wurde die beschädigte Lage von dem Neurologen unseres Projektes in Form von vier allgemeinen Stufen des zentralen Nervensystems angegeben. Diese eingeteilten Stufen der Beschädigung wurden bei der Analyse der auditorischen und vestibulären Daten in Betracht gezogen.

Die Serie der auditorischen Tests bestand aus den üblichen Prüfungen der Ton- und Sprachschwelle, aus einer Fähigkeitsprüfung einsilbige Wörter zu unterscheiden so-wie aus einer Reihe von besonderen Ton- und Sprachprüfungen.

Die 6 besonderen Tonproben, die zur Anwendung gekommen sind, umfassten Prüfungen der Anpassung, der Lautheitsfunktion und kurzer Zunahmempfindlichkeit sowie drei Untersuchungen der binauralen auditorischen Funktion.

Die vier Sprachuntersuchungen enthielten die Proben des Unterscheidungsvermögens von einsilbigen Wörtern bei ipsilateralem Weisslärm, im Gegensatz zu kontralateraler Wettbewerbssprache, in den verschiedenen filterten Arten und unter verschiedenen binaural maskierenden Situationen.

Die vestibulären Bewertungen umfassten vier hauptsächliche Arbeitsmethoden nämlich eine Gruppe von Tests, die sich mit visuellen induzierten Augenbewegungen einer Kontrolle des Spontannystagmus, der Suche nach dem Lagenystagmus und einer Überprüfung der Erwiderung zur Kalorien-erregung befasste. Alle Bewertungen wurden mit Hilfe von Elektronystagmographie ausgeführt.

Sowohl einzeln als auch in dem Umfang in dem sie zu einem Ergebnis modell gehörten wurden die Resultate betrachtet. Die neurologischen Bewertungen der 61 Versuchspersonen enthüllten, im allgemeinen, Symptome, die multiple Stufen — Schäden vom zentralen Nervensystem, insbesondere vom Mittelhirn und Hirnstamm vermuten lassen. Auditorische Bewertungen bewiesen eine ausgezeichnete Mannigfaltigkeit auditorischer Aberrationen, die meistens durch Untersuchungen, die zum anhaltenden Anreiz eine Reaktion erforderte, die Sprachunterscheidung in der abnormalen Bedingungen sowie die binauralen maskierenden Proben, bestimmt wurden. Auch die vestibulären Bewertungen zeigten eine gleichartige Veränderung in den Ergebnissen, die bemerkenswert waren. Unter den gewöhnlichsten Erkenntnissen waren abnormale visuell induzierte Augenbewegungen, Lagenystagmus und Übererregbarkeit als Antwort auf den Kalorien-anreiz.

audiological procedures will eventually come to have unique value in assisting in the identification of sclerotic pathology in the living person

Second remember that involvement of the VIIIth nerve trunk appeared to be relatively rare in the group of patients with multiple sclerosis under study Most of the distinctive auditory symptomatology these individuals exhibited is consequently attributable to disturbances within the central auditory nervous system Much of this symptomatology mimicked responses traditionally associated with inner ear lesions although some mimicked behavior induced by VIIIth nerve pathology Clearly it becomes necessary to rethink the diagnostic significance of the entire array of auditory tests when CNS lesions such as multiple sclerosis are a possibility This does not mean that test findings do not have the conventional meanings when encountered in the presence of peripheral auditory diseases and disorders It does mean that the same findings can have new meanings when CNS lesions are present Here too is an area where the further study of the auditory behavior of multiple sclerotic subjects coupled with good supporting data should prove most productive

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From the Auditory Research Laboratory
Northwestern University Evanston, Illinois, USA

UPPSALA 1972

CONTENTS

Present Address of Z. G. Schoeny:
Department of Audiology and Speech Pathology
University of Virginia, Charlottesville, Virginia, USA

Address for correspondence:
Dr. Peter Dallos, Northwestern University
Speech Annex Building, Evanston, Illinois 60201, USA

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Abstract

An extensive parametric study was conducted on the stimulus-related dc potentials of the cochlea (summating potential, SP). The potentials were measured from all three cochlear scalae, vestibuli (SV), tympani (ST) and media (SM) from the first three turns of guinea pig cochleae. Results are shown in terms of the potential gradient across the cochlear partition [DIF = SV − ST] and the common-mode potential of the perilymphatic space [AVE = (SV + ST)/2], as well as for the individual active electrodes. Aside from magnitude information, waveform patterns of the DIF, AVE, and SM potentials are also presented as functions of stimulus parameters. It is shown that there is a "best" frequency for any electrode location where at any stimulus level the DIF and SM responses are negative and the AVE response is positive. Below the best frequency the DIF and SM components are generally positive, while they vanish at higher frequencies. The AVE response is negative everywhere except within the best frequency region. The best frequency is approximately one octave above the frequency of the traveling wave maximum for a given cochlear site. Some preliminary hypotheses about the genesis of the various SP components are provided.

of important observations on SP. They recorded from the scala media of guinea pig cochleas with micropipettes, the reference electrode being in the scala tympani. They noted that upon passing through the organ of Corti with the pipette at the point of encountering the positive EP a polarity reversal of the SP occurred together with a phase inversion of the CM. This suggested to the authors, just as similar earlier observations on the CM suggested to Tasaki et al. (1954) that the potentials that reverse phase or polarity must be generated at the level where reversal takes place, that is, at the cilia bearing ends of the hair cells. It is unfortunate that Konishi & Yasuno did not elaborate on the experimental conditions that prevailed while the polarity reversal was observed. Specifically they did not indicate what the stimulus frequency or intensity were, or if these parameters could be varied while still obtaining the same result. Konishi & Yasuno also used polarizing currents to alter the SP response. Their results were quite complex and hard to interpret. One of their most important contributions was their attempt to obtain some parametric data on SP. They recorded input–output functions from the basal turn at eight different frequencies, and also SP vs frequency functions from all four turns at a constant (but unspecified) intensity. These functions reveal that the response tends to be negative in the turn that is most sensitive to the stimulus frequency. It also shows, contrary to earlier reports, that for frequencies that stimulate rather distant areas from the recording site the response is a large positive one. Butler et al. (1960) noted that the SP had a negative temperature coefficient as opposed to the normal positive temperature coefficient manifested by CM and EP. This observation suggested that the processes that generate CM and SP are different. Stopp & Whitfield (1964) made the important observation that the summating potential that could be recorded from the pigeon's cochlea had similar properties to the SP that was obtained from mammalian cochleas. Specifically, both SP+ and SP− were recordable. Since in the avian cochlea inner and outer hair cells are undifferentiated, Stopp & Whitfield's data mitigate against the hypothesis that the two different polarity SP are produced by different groups of hair cells. An important theoretical contribution to the problem of the SP production was made by Whitfield & Ross in 1965. These authors contend that the SP results from the nonlinearity of the CM generators, in other words, that it is merely the first component in a Fourier series that describes microphonic distortion. They noted that the apparent large size of the SP compared to the fundamental CM component, and even more so compared to higher harmonic components in CM, made the acceptance of the straightforward distortion hypothesis tenuous. In order to deal with this difficulty these authors postulated that due to the fact that a recording electrode picks up from a finite segment of the cochlea, and that within this segment there is a gradual phase change of the stimulus (i.e. of the traveling wave), CM generators contributing to the overall response are generally not in phase. The higher the frequency the more rapid is the phase change. Since the CM voltages sum vectorially at the electrode location, high frequency responses will suffer an apparent diminution due to cancellations among out-of-phase generators. Such cancellation of course does not affect the SP, thus it is conceivable that the apparent size of the distortion component (SP) might be observed as being bigger than the distorted signal (CM) from which the former is derived in the process of nonlinear distortion. This ingenious argument certainly makes it possible to accept the distortion hypothesis for the genesis of SP at least for certain portion of the SP. The distortion hypothesis was further espoused by Johnstone & Johnstone (1966) and by Engebretson & Eldredge (1968). The former authors derived a mathematical model for the generation of the SP; they showed that sinusoidal motion of the basilar membrane would always yield asymmetrical displacement of the cilia, and thus the means of producing SP. Another contribution was made by the latter authors who studied simple electrical models and demonstrated that

Introduction

In 1950 Davis, Fernández & McAuliffe and Békésy independently noted that a tonal stimulus can elicit a dc potential change in the cochlea During the decades following its discovery this dc cochlear response has been the subject of numerous investigations. These studies have clarified many properties of the response, but the most pervasive motif in the literature concerns the elusiveness of this potential and its propensity to defy quantification The best illustration of this fact in that it took nineteen years from its discovery for some published data to appear on the quantitative properties of the summating potential (SP) as this dc response became known over at least some range of pertinent parameter values (Honrubia & Ward 1969). The pioneering investigations of Davis and his colleagues culminated in a qualitative treatment of the subject (Davis et al., 1958*a*)

Apparently the major difficulty in settling the SP problem stems from the non unitary nature of this response. It was realized quite early that the SP is probably the sum of various components, originating in different physiological sites and processes (Davis et al., 1952 Goldstein 1954) Later only two components were emphasized, a positive (SP+) and a negative (SP−) summating potential (Davis et al 1958*a*) In their original communication Davis et al (1950) proposed that the SP is the electrical sign of the local excitatory process in the cochlear dendrites, that is excitatory postsynaptic potential (EPSP) While Davis et al. (1952) did extensive recordings with various combinations of intracochlear electrodes (such as scala tympani vs. vestibuli vestibuli vs indifferent, tympani vs. indifferent and intramodiolus vs. indifferent) they did not fully exploit the information contained in the comparison of responses obtained from the various combinations of recording sites. As we will attempt to demonstrate later such information might be the crucial factor in the unraveling of the complexities of the SP In 1957 Misrahy et al addressed themselves to the very pertinent problem whether or not the SP was a true physiological response or whether it might have been merely due to electrochemical reactions of the recording electrodes in the presence of loud sounds, or due to other artifactual conditions. They concluded that the SP was indeed a physiological response It was noted however that surgical injury such as escape of perilymph from the cochlea seemed to potentiate SP production. Because of this, they suggested that the " major factor influencing the summating potential maybe even its source is distortion within the cochlea." (p 4)

From a study of cochlear potentials modified by streptomycin poisoning and by venous obstruction, emerged the novel suggestion that the negative SP (as measured in scala media or scala vestibuli of the first turn of guinea pig cochleas) was primarily produced by the inner hair cells, while positive SP along with CM was assigned to the outer hair cells (Davis et al., 1958*b*) A summary paper by Davis et al (1958*a*) collected all known information about the SP The effect of anoxia upon cochlear potentials was extensively studied by Konishi et al (1961) Kiang & Peake (1960) introduced two interesting new methods into the study of SP using denervated cat cochleas as recording sites, and averaging computer techniques They noted that normal SP was not affected by the integrity of the cochlear nerve supply The authors also studied a "slow potential" that could be recorded at low sound intensities, and which was thought to be different from Davis SP Presumably this "slow potential is the same as SP In 1963 Konishi & Yasuno presented a number

of important observations on SP. They recorded from the scala media of guinea pig cochleas with micropipettes, the reference electrode being in the scala tympani. They noted that upon passing through the organ of Corti with the pipette at the point of encountering the positive EP a polarity reversal of the SP occurred together with a phase inversion of the CM. This suggested to the authors, just as similar earlier observations on the CM suggested to Tasaki et al. (1954) that the potentials that reverse phase or polarity must be generated at the level where reversal takes place, that is, at the cilia-bearing ends of the hair cells. It is unfortunate that Konishi & Yasuno did not elaborate on the experimental conditions that prevailed while the polarity reversal was observed. Specifically they did not indicate what the stimulus frequency or intensity were, or if these parameters could be varied while still obtaining the same result. Konishi & Yasuno also used polarizing currents to alter the SP response. Their results were quite complex and hard to interpret. One of their most important contributions was their attempt to obtain some parametric data on SP. They recorded input-output functions from the basal turn at eight different frequencies, and also SP vs frequency functions from all four turns at a constant (but unspecified) intensity. These functions reveal that the response tends to be negative in the turn that is most sensitive to the stimulus frequency; it also shows, contrary to earlier reports, that for frequencies that stimulate rather distant areas from the recording site, the response is a large positive one. Butler et al. (1960) noted that the SP had a negative temperature coefficient as opposed to the normal positive temperature coefficient manifested by CM and EP. This observation suggested that the processes that generate CM and SP are different. Stopp & Whitfield (1964) made the important observation that the summating potential that could be recorded from the pigeon's cochlea had similar properties to the SP that was obtained from mammalian cochleas. Specifically both SP+ and SP− were recordable. Since in the avian cochlea inner and outer hair cells are undifferentiated, Stopp & Whitfield's data mitigate against the hypothesis that the two different polarity SP are produced by different groups of hair cells. An important theoretical contribution to the problem of the SP production was made by Whitfield & Ross in 1965. These authors contend that the SP results from the nonlinearity of the CM generators. In other words, that it is merely the first component in a Fourier series that describes microphonic distortion. They noted that the apparent large size of the SP compared to the fundamental CM component, and even more so compared to higher harmonic components in CM, made the acceptance of the straightforward distortion hypothesis tenuous. In order to deal with this difficulty these authors postulated that due to the fact that a recording electrode picks up from a finite segment of the cochlea, and that within this segment there is a gradual phase change of the stimulus (i.e. of the traveling wave), CM generators contributing to the overall response are generally not in phase. The higher the frequency, the more rapid is the phase change. Since the CM voltages sum vectorially at the electrode location, high frequency responses will suffer an apparent diminution due to cancellations among out-of phase generators. Such cancellation of course does not affect the SP; thus it is conceivable that the apparent size of the distortion component (SP) might be observed as being bigger than the distorted signal (CM) from which the former is derived in the process of nonlinear distortion. This ingenious argument certainly makes it possible to accept the distortion hypothesis for the genesis of SP, at least for certain portion of the SP. The distortion hypothesis was further espoused by Johnstone & Johnstone (1966) and by Engebretson & Eldredge (1968). The former authors derived a mathematical model for the generation of the SP; they showed that sinusoidal motion of the basilar membrane would always yield asymmetrical displacement of the cilia, and thus the means of producing SP. Another contribution was made by the latter authors who studied simple electrical models and demonstrated that

Introduction

In 1950 Davis, Fernández & McAuliffe and Békésy independently noted that a tonal stimulus can elicit a dc potential change in the cochlea During the decades following its discovery this dc cochlear response has been the subject of numerous investigations. These studies have clarified many properties of the response but the most pervasive motif in the literature concerns the elusiveness of this potential and its propensity to defy quantification The best illustration of this fact in that it took nineteen years from its discovery for some published data to appear on the quantitative properties of the summating potential (SP) as this dc response became known, over at least some range of pertinent parameter values (Honrubia & Ward 1969). The pioneering investigations of Davis and his colleagues culminated in a qualitative treatment of the subject (Davis et al 1958*a*)

Apparently the major difficulty in settling the SP problem stems from the non unitary nature of this response It was realized quite early that the SP is probably the sum of various components, originating in different physiological sites and processes (Davis et al 1952 Goldstein 1954) Later only two components were emphasized a positive (SP+) and a negative (SP−) summating potential (Davis et al 1958*a*) In their original communication Davis et al (1950) proposed that the SP is the electrical sign of the local excitatory process in the cochlear dendrites, that is excitatory postsynaptic potential (EPSP) While Davis et al (1952) did extensive recordings with various combinations of intracochlear electrodes (such as scala tympani vs vestibuli, vestibuli vs. indifferent tympani vs. indifferent and intramodiolus vs. indifferent) they did not fully exploit the information contained in the comparison of responses obtained from the various combinations of recording sites. As we will attempt to demonstrate later such information might be the crucial factor in the unraveling of the complexities of the SP In 1957 Misrahy et al addressed themselves to the very pertinent problem whether or not the SP was a true physiological response or whether it might have been merely due to electrochemical reactions of the recording electrodes in the presence of loud sounds, or due to other artifactual conditions They concluded that the SP was indeed a physiological response it was noted however that surgical injury such as escape of perilymph from the cochlea seemed to potentiate SP production Because of this, they suggested that the major factor influencing the summating potential maybe even its source is distortion within the cochlea. (p 4)

From a study of cochlear potentials modified by streptomycin poisoning and by venous obstruction, emerged the novel suggestion that the negative SP (as measured in scala media or scala vestibuli of the first turn of guinea pig cochleas) was primarily produced by the inner hair cells, while positive SP along with CM was assigned to the outer hair cells (Davis et al 1958*b*) A summary paper by Davis et al (1958*a*) collected all known information about the SP The effect of anoxia upon cochlear potentials was extensively studied by Konishi et al (1961) Kiang & Peake (1960) introduced two interesting new methods into the study of SP using denervated cat cochleas as recording sites and averaging computer techniques They noted that normal SP was not affected by the integrity of the cochlear nerve supply The authors also studied a slow potential" that could be recorded at low sound intensities, and which was thought to be different from Davis SP Presumably this slow potential is the same as SP In 1963 Konishi & Yasuno presented a number

recording from the perilymphatic scalae we have paid attention not only to the dc potential difference across the cochlear partition (the only potential that had interested earlier investigators), but also to the common dc potential of the two scalae. This common or average (AVE) potential component has evolved in the course of our studies as being just as significant as the potential gradient (Dallos et al., 1970), thus our data show that the common assumption that the SP polarity is opposite in scala vestibuli and tympani is not generally tenable. Aside from obtaining the two potential components (gradient and average) we have also compared these with the dc potentials recordable from scala media. Throughout the investigation we have used computer averaging methods that permitted data collection over a very wide range of signal intensities. Finally the total number of animals used in this experimental series (over 75) was large enough to permit us to report central tendencies in the data.

In the present report we wish to concentrate on the simple, quantitative description of the summating potential The identification of the sources of the various subcomponents will comprise the subject of a future publication.

a number of nonlinear electrical phenomena that were known to exist in the cochlea (SP combination tone production and the interference effect) can be accounted for by the same nonlinearity Engebretson & Eldredge also suggest which we believe is a key point, that several nonlinear processes probably coexist in the cochlea, and these processes can account for the various (hard to reconcile with a single source hypothesis) properties of the SP Kupperman (1966) further elaborated on the non unitary nature of SP He recorded from the scala tympani of all four turns of the guinea pig cochlea and focused his attention on the interaction between and the nature of the positive and negative SP He contends that the positive SP recorded from scala tympani (with the reference electrode in indifferent tissue) *from which the negative SP is subtracted out* would show strong localization to the site of maximum excitation This potential (pure positive SP as he called it) was regarded by Kupperman to be a manifestation of current flow between scalae media and tympani in the region of maximum stimulation. He regarded the negative SP in the scala tympani to be a sign of summated asynchronous neural potentials

Davis the discoverer of SP now regards it " as an incidental byproduct arising from asymmetry in the mechanism that produces cochlear microphonic rather than as a major physiological mechanism (Davis, 1968 p 652) Others are not so pessimistic about the possible function and significance of the SP Honrubia & Ward (1969) have recently completed a significant parametric study of the SP and they conclude that the negative SP is likely to act as a stimulus to the VIIIth nerve while the positive SP would probably be inhibitory These authors recorded SP with fine pipettes from the scala media in all four turns of the guinea pig cochlea. They varied signal intensity frequency and duration It was found that SP magnitude increased linearly with log-duration. The authors provided a number of plots giving the longitudinal distribution of SP as the function of stimulus frequency and intensity The familiar relationship again emerges that in the region of maximum stimulation the SP is *negative* *In all turns the* SP elicited by tones whose frequency was considerably below that favorable to the electrode location, the SP started out positive, went through a maximum with increased sound intensity decreased toward zero and finally turned negative at very high intensities. Those frequencies which were favorable to the electrode location elicited negative SP s even at relatively low intensities. One of the major limitations of this otherwise excellent study is that for technical reasons no data were obtained at low sound intensities (below approximately 65 dB)[1]

The review of the SP literature indicates that while there are salient properties of this potential about which there is a fairly general agreement, there are other aspects of this phenomenon *that are still unresolved* *Except for the data of* Konishi & Yasuno (1963), Honrubia & Ward (1969) and Kupperman (1966) most studies have been confined to studying the SP at high frequencies and high intensities The former two of these more complete investigations confined themselves to scala media recording, while the latter to describing scala tympani data There is a tacit assumption running through the entire literature that the SP is of oppposite polarity in scala vestibuli and tympani There is a severe paucity of information on the low intensity behavior of the SP Our work was designed to provide quantitative information on the properties of the SP from all three scalae of the first three turns of the guinea pig cochlea for a wide range of stimulus parameters. Since the SP is *apparently a multi-component* response, and since there is a very real probability that some of the components might play an important intermediary role in the process of peripheral information transfer we decided to reevaluate the entire SP phenomenon Aside from the purpose to provide extensive parametric information we have also endeavored to utilize recording techniques that enabled us to shed new light on this *stimulus-related dc* potential Specifically when

[1] All sound pressures in this paper are expressed in dB re 0.0002 dyne/cm²

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Methods

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We have evaluated the possible effect of electrode polarization, by recording dc potentials from the cochlea with Ag AgCl and Tungsten electrodes placed within one millimeter from one-another in the basal turn. The Ag–AgCl electrodes usually recorded a slightly greater dc potential magnitude, but for the stimulus parameters used in this study there was no discernible difference in the dynamic properties of the recorded response between the two electrodes. For this reason, and because tungsten electrodes can be made smaller and they are easier to fabricate these were used primarily during routine measurements from the perilymphatic scalae.

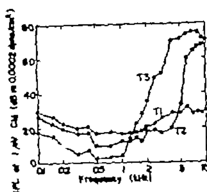


Fig. 1. Median CM isopotential curves (sound pressure level required to produce 1 μV rms CM potential) obtained with differential electrodes from the three turns of the cochlea. The medians are based on 31 animals from turn-one, 13 from turn-two, and 18 from turn-three.

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Before the results are described a terminology that is used throughout this paper must be introduced. When potentials are recorded from scala vestibuli or from scala tympani with reference to an electrode in indifferent tissue (the neck muscles) these will be denoted as SV and ST potentials respectively. The potentials can be combined to yield two different kinds of information. When the difference $DIF = SV - ST$ or the sum $AVE = (SV + ST)/2$ are formed,

In our first report on this subject (Dallos et al., 1970) we defined the difference component in a somewhat different manner namely we had $DIF = (SV-ST)/2$. The reason for this choice was that when CM is recorded with differential electrodes in a situation where the stimulus frequency is tonotopically coincident with the electrode location, then the CM magnitude recorded from either scalae vestibuli or tympani is one-half of what is recorded with both electrodes connected to a differential amplifier. The introduction of the compensating factor of one-half is not really necessary since as one can appreciate with the circuit of Fig. 2a, the individual electrodes in this case record voltage drops that are one-half of the source voltage. Consequently the actual potential gradient, reflected by the differential electrode output, is a better representation of the source voltage than the single electrode response.

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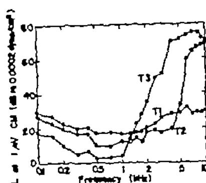


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evaluated by taking the difference between the baseline and the average magnitude of the SP during the final five milliseconds of the response. For SM recordings, where the response had not reached its final value by the end of the 60 msec duration of the stimulus, the SP was measured as the difference between the baseline and the actual value of the response at the cessation of the signal.

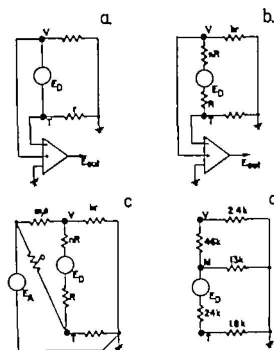


Fig 2 Various equivalent electrical circuits that are discussed in the text In all four circuits the same symbols are used the nodes *T V* and *M* designate the recording points in scalae tympani, vestibuli and media, the generator E_D symbolizes the voltage source within the organ of Corti, while E_A is an extra-partition remote source (*a*) Equivalent circuit of a completely symmetrical differential electrode recording situation. The voltage at node *V* is $E_D/2$, while at node *T* it is $-E_D/2$. Hence the voltage differential $\mathrm{DIF} = E_{OUT} = E_V - E_T = E_D$. (*b*) Schema of the differential electrode recording scheme when the various circuit elements are asymmetrical (*c*) Simplified scheme of the differential electrode recording scheme when both local and remote sources are active and when all circuit elements are asymmetrical (*d*) Equivalent circuit of a cochlear cross section. Resistance values after Johnstone et al., 1966.

these are analogous to the potentials obtained classically with the differential electrode technique when AP or CM are respectively minimized The usual interpretation of the results of the differential electrode recordings under those two conditions is that the former emphasizes the local response (different polarity for the two electrodes across the cochlear partition) or the remote response (same polarity for the two electrodes), (Tasaki et al 1952 Teas et al 1962) For our purposes these potentials, DIF and AVE, are construed as follows. The DIF potential is proportional to the potential difference across the cochlear partition and to a good approximation this quantity describes the *locally generated voltage* that is one whose source is located between the electrode tips. The AVE response is proportional to the *common potential* of the two scalae Ordinarily this response is associated with remote activity but aside from this, we tend to look at this potential as either being proportional to a voltage drop created by longitudinal current flow which is in the same direction in both scalae vestibuli and tympani or one that reflects the asymmetry of cochlear electroanatomy or both. Both operations, $\mathrm{DIF} = \mathrm{SV} - \mathrm{ST}$ and $\mathrm{AVE} = (\mathrm{SV} + \mathrm{ST})/2$ can be, and have been performed either electronically during the experiment, or graphically or arithmetically from the SV and ST data. Either method yields essentially the same result. We are presenting data on the pages to follow in both forms SV and ST or DIF and AVE. When either form is given the other can be obtained by simple computation The relative independence of the DIF and AVE components is considered in detail in the Discussion section of this paper It will be emphasized that it is difficult to reliably record one of these components if it is small provided that the other component is very large We will see for example that the DIF component that is recorded from the higher cochlear turns at high frequencies is quite small and does not seem to show a clear pattern of change with signal parameters. At the same time the AVE component is rather large In this situation the DIF component that one records is probably nothing more than an artifact resulting from imperfect electrode placement The greater the disparity between DIF and AVE is in a given recording situation the more reliable the recording is for the larger and the less reliable it is for the smaller component

The final comment in this section concerns the actual evaluation of the data. The SP information was obtained from the averaging computer in the form of X–Y plots that is, SP magnitude plotted as the function of time Since the SP waveform changes during the presence of the stimulus it was necessary to establish a set procedure for obtaining the SP magnitude from the plots All SV ST DIF and AVE data were

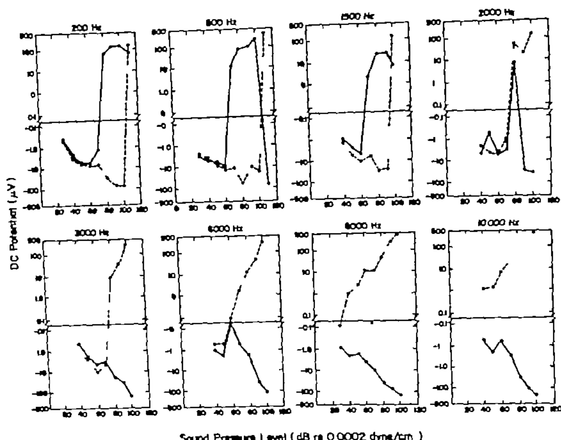


Fig. 3. Median SP input-output functions at various frequencies from scala vestibuli (●—●) 2nd scala tympani (○—○) of the first cochlear turn

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The exceptional frequency is 10 000 Hz where the average potential of the two scalae is positive at *all* intensities. The DIF plots depict a complete and orderly transition from low to high frequencies. At 200 Hz the local response is positive at all SPLs, while it is negative at all SPLs at the highest frequency tested. In between a transition takes place in that at high intensities the DIF potential turns negative, this occurs at lower intensities as the frequency increases. It

Results

MAGNITUDE AND POLARITY OF THE SP

Unless otherwise indicated the plots depicting SP magnitude as the function of various parameters are median plots. Data points are obtained as the median value of individual data that are available for a given experimental condition. The number of experimental animals that contribute to a given median datum is not the same fewer points are available at the extremes of the intensity range for example, and fewer points from the third cochlear turn than from the first. The range of the number of animals whose responses were used for obtaining a given point was between 3 and 19 the majority being between 5 and 7

Let us first consider the response patterns in the form of input–output functions, that is SP magnitude versus sound intensity at any given frequency and electrode location. In Fig. 3 a set of such functions is shown for basal turn electrodes, both SV and ST responses are included The eight pairs of plots depict the variation of SP as the frequency changes from 200 to 10 000 Hz and as the signal intensity changes between 40 and 100 dB sound pressure level (SPL) Note that these are log–log plots the ordinate gives the SP magnitude in μV over a ± 80 dB range, while the abscissa is expressed in dB re 0 0002 dyne/cm² At 200 Hz, below 70 dB SPL, *both* SV and ST electrodes register negative potentials, moreover below 60 dB they see approximately the same potential magnitude Above 70 dB the SV potential turns positive while the ST potential remains negative Above approximately 80 dB the absolute value of the SV potential exceeds that of the ST one If the sound intensity is further increased beyond 100 dB SPL, another polarity reversal can be seen at approximately 110 dB the ST potential goes positive and at even higher SPL s the SV potential would go negative The picture then would be similar to what is seen for 500 Hz. At this latter frequency the character of the response is quite like that at 200 Hz at very low SPLs both electrodes see about equal negativity around 70 dB the SV electrode becomes positive but here a second reversal occurs within the depicted range. At approximately 105 dB both scalae reverse their polarity As stimulus frequency further increases, the pattern seen for 500 Hz undergoes a gradual change into the pattern shown for the 3 000 Hz condition This change involves the disappearance of the positive hump for the SV electrode which is now negative at *all* SPLs, and the gradual lowering of the cross over point of the ST potential Note that here as well as in the following plot (for 6 000 Hz) we still see *both* scalae at the approximately identical negative potential level at the lowest intensities. Attention is called to the very consistent slight inflexion or reversal in the SV potential plot at approximately 60 dB which is of course the level where this scala turned positive at lesser frequencies. The overall pattern seen at 3 000 Hz continues at 6 000 Hz, the only difference is that the ST-cross over occurs at a lower intensity This process continues as frequency is raised until as shown in the 8 000 Hz plot the SV is negative while the ST is positive at all intensity levels. The 10 000 Hz plot is almost identical at least it appears so actually there are important albeit subtle differences between them as will be seen in the DIF and AVE plots of these same data

The plots of Fig. 3 reveal a very consistent and systematic shift in the SP pattern from low to high frequencies and from low to high intensities. The following salient features are worth mentioning. At very high intensities, irrespective of frequency the basal SV potential is negative the basal ST potential is positive This observa

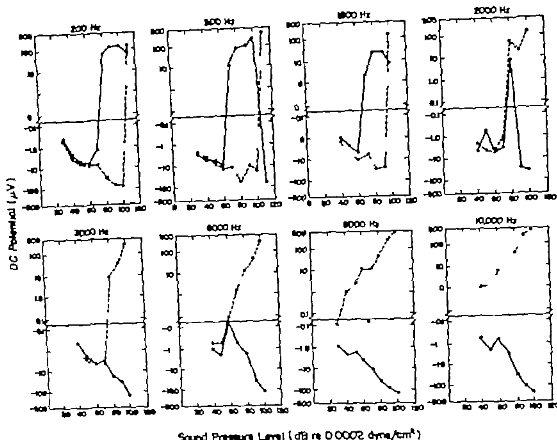


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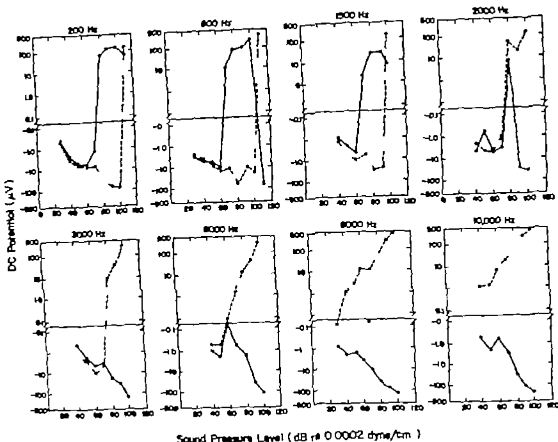


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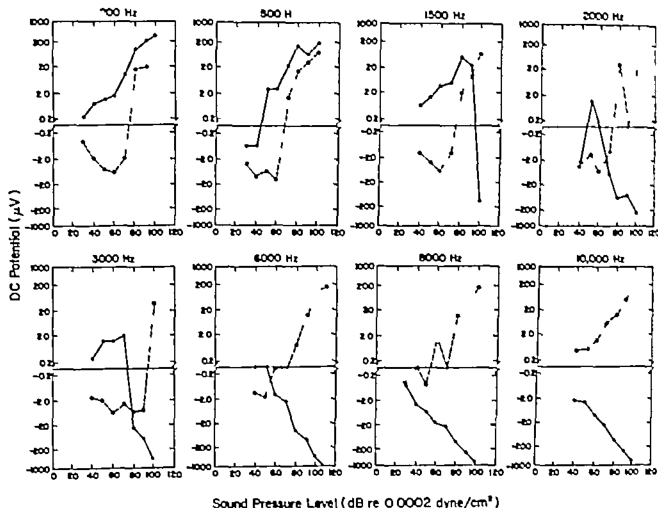


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Let us now turn our attention to SP data recorded from the second turn of the guinea pig s cochlea Again a series of input-output functions are shown in Fig 5 for both the SV and ST electrodes. These plots appear somewhat more complex than those for the first turn, but close scrutiny reveals that very systematic changes in the SP exist here too with variation of both fre-

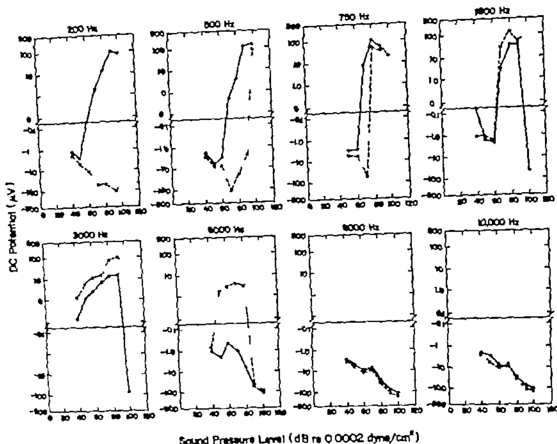


Fig. 5. Median input-output functions at various frequencies from scala vestibuli (●—●) and scala tympani (○ – ○) of the second cochlear turn

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The ST potential exhibits a progressive change from 200 to 3 000 Hz. Below 500 Hz the ST potential is always negative. At 500 Hz the ST potential turns positive at 90 dB SPL, the turnover occurs at about 75 and 65 dB between 750 and 1 500 Hz, while at 3 000 Hz the ST is always positive. At 1 500 Hz we see another trend develop, the SV potential goes negative at high intensities, by 6 000 Hz it is always negative even though a clear transition between two zones is seen at 60–70 dB. At *8 0000* and 10 000 Hz both electrodes are measuring approximately equal negative potentials that gradually increase with stimulus intensity. Here again we must point out that the data clearly show that the two scalae of the same turn do not always have potentials of opposite polarity. In fact, at low frequencies and low intensities the two scalae are about equally negative, and at high frequencies at all intensities the two scalae are again about equally negative. At very low frequencies and at relatively high intensities the SV is positive, the ST is negative, while if we would have shown in this figure potentials for

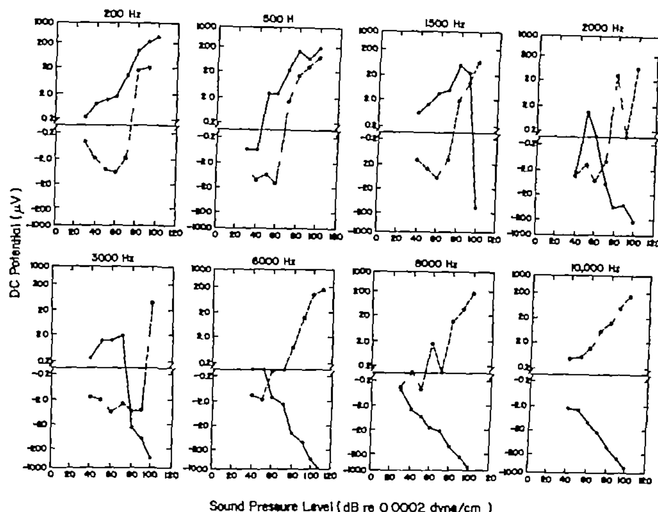


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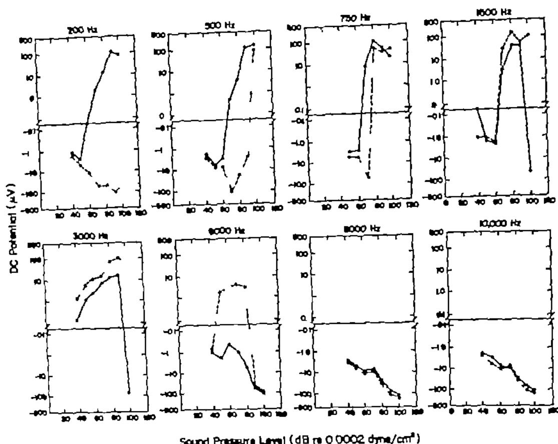


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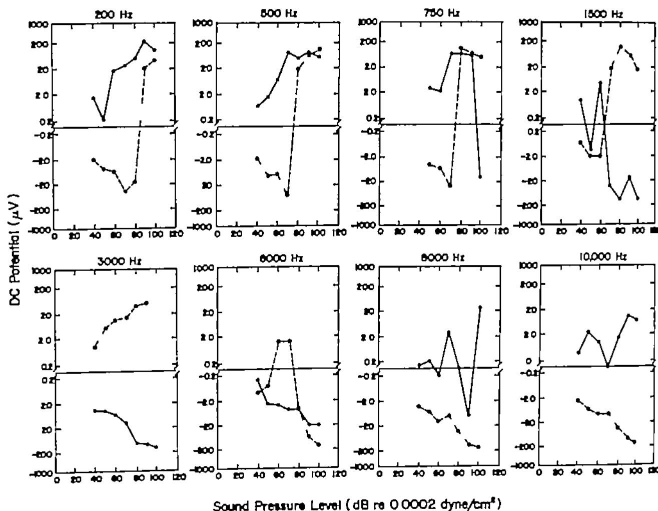


Fig 6 Median SP input–output functions at various frequencies from the second cochlear turn Plots are given for the DIF (●—●) and AVE (○—○) components.

intensities well above 100 dB we would have seen an additional reversal at low frequencies, whereby the SV would have become negative, the ST positive It is remembered that this situation is very much as that seen in the basal turn.

When the data are recast to show local DIF and common AVE responses, we obtain Fig. 6 At the lowest frequencies the local response is small at low sound levels, and is positive at higher intensities The AVE response at these low frequencies starts out negative increases its magnitude then crosses over into the positive region at progressively lower and lower SPL s as frequency is increased At 750 Hz we notice the beginning of another trend The DIF response starts to move negative, first at high SPLs only but by 3 000 Hz it is negative at all levels Above 3 000 Hz the DIF response becomes smaller and by 8 000 and 10 000 Hz it is negligible [1] The initial negativity of the AVE

[1] It is important to explain, and to clearly understand the contention that the DIF component is negligible in the 8 and 10 kHz plots. To do this, attention is called to the Discussion concerning expected errors in DIF or AVE components whenever one of these components is considerably in excess of the other When such disparities exist, the smaller of the two components cannot be measured accurately if even minor asymmetries are present between SV and ST recordings. One almost invariably must contend with such asymmetries, thus the safest procedure is to disregard a component if it is much smaller than the other and if this component appears to fluctuate unsystematically about zero voltage. The DIF component at 8 and 10 kHz has these characteristics, it is most likely not a true response but merely a manifestation of experimental error This contention can be underscored by examining the individual electrode responses at these

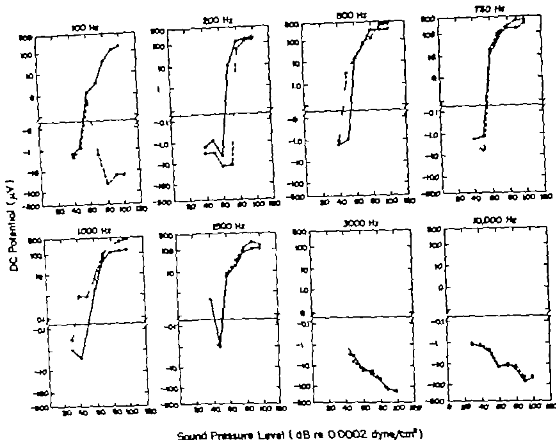


Fig. 7. Median input–output functions at various frequencies from scala vestibuli (●—●) and scala tympani (○—○) of the third cochlear turn

response becomes less and less pronounced as frequency increases between 500 and 1 500 Hz, and at 3 000 Hz this response component is positive at all intensities. Above 6 000 Hz the AVE response reverses once again, and at the highest frequencies it is uniformly negative.

Let us now turn to recordings from the third turn, first the potentials from SV and ST are examined then DIF and AVE components are discussed. In Fig. 7 the potentials seen by the individual electrodes are shown in the now familiar format of input–output functions. The first, very striking observation is that in contrast with recordings from the lower turns, where in general the two electrodes picked up considerably different potentials, here they tend to see similar responses. At the lowest frequencies the responses from both electrodes are negative and approximately equal at low intensities. This behavior we recall is the same in all three turns. The SV electrode turns positive at approximately 60 dB SPL up to 1 000 Hz, above that this positivity eventually disappears. The ST electrode shows a considerable change at low frequencies at 100 Hz it is negative at the lowest and highest intensities, with the increase in frequency it goes positive at the mid-intensities. At 3 000 Hz and above, both electrodes are negative and equal in potential magnitude

The DIF and AVE plots (Fig. 8) show that

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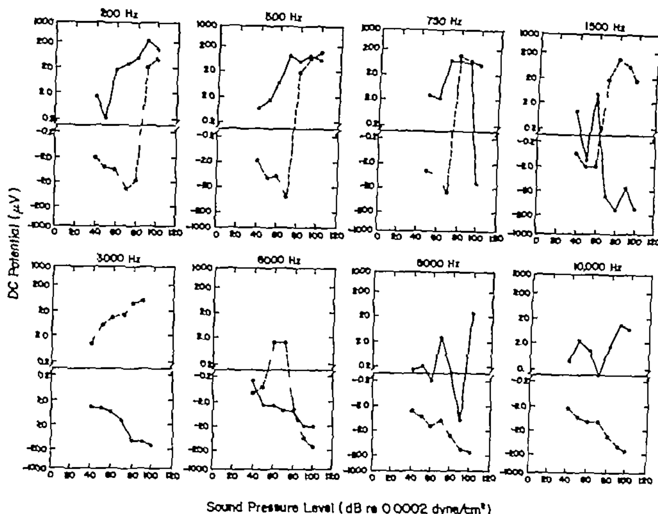


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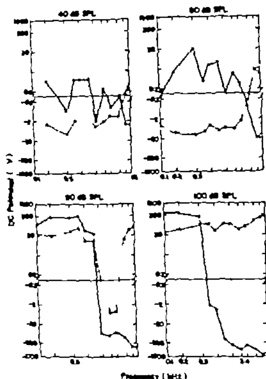


Fig. 9. Median SP versus stimulus frequency functions at several signal intensities from the first cochlear turn. Plots are given for the DIF (●—●) and AVE (○—○) components.

to sufficiently high frequencies. The zone of major importance is the one around the best frequency of the recording electrode. In this zone the local response is negative. The best frequency could be identified by the maximum response point on the plot depicting the lowest intensity condition. Accordingly, 10 000, 3 000 and approximately 1 000 Hz are identified as the best frequencies for turns 1, 2, and 3 respectively.[1] The frequency region of negativity widens with increasing stimulus level. This effect is the most dramatic in the basal turn, where the low frequency crossover from negative to positive response shifts from 6 000 Hz at 50 dB to approximately 700 Hz at 100 dB SPL. The second frequency region of interest is below the band of negativity. Here, at low frequencies, the response from all turns appears to be positive. Of course, as intensity increases and the negative band becomes wider, the positive band narrows. The third region of interest is encompassed by frequencies above the band of negative responses. For these high frequencies the DIF response component is small in comparison with the AVE potential. In contrast with the radical intensity dependence of the boundary between the positive and negative response regions, the high frequency boundary of the negative response changes only moderately with intensity. There is a general widening of the active region with increasing intensity, but it appears that beyond a certain frequency the response is always very small, no matter how high the stimulus intensity might be. Eight to nine thousand hertz is such a boundary for turn-two, while approximately 4 000–6 000 Hz is the limit for the active zone in turn-three.

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[1] The absolute maximum of the DIF component in the first turn is achieved at approximately 15 000 Hz.

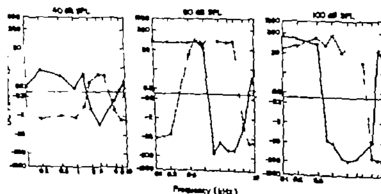


Fig. 10. Median SP versus stimulus frequency functions at several signal intensities from the second cochlear turn. Plots are given for the DIF (●—●) and AVE (○—○) components.

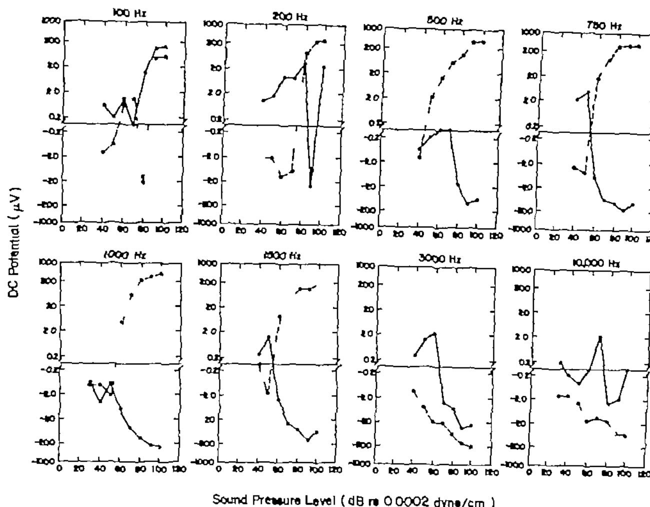


Fig 8 Median SP input–output functions at various frequencies from the third cochlear turn. Plots are given for the DIF (●—●) and AVE (○—○) components.

the local response is positive at the lowest frequencies in conformity with the results obtained from turns 1 and 2. The AVE response is negative at the low intensities at all frequencies, it becomes positive at higher intensities at low frequencies, and finally at high frequencies it is negative at all intensities. The DIF response becomes negligible at high frequencies, in the region of the best frequency (the exact frequency is missed in this series) it tends to be negative, while at that same frequency the AVE response is positive

All the contentions that were obtained from *input–output functions* can be put in even better perspective by examining some of the data in a different manner Instead of input–output functions, the results can be presented in the form of tuning curves, that is as SP versus frequency with intensity as the parameter In Figs. 9 10 and 11 such functions are shown for all three turns both for the DIF and the AVE components Only plots for a few intensities are shown, generally for one low one moderate and for one high SPL condition For the plots depicting the basal turn response an extra intensity level (90 dB) is also given for reasons that will become clear below

Let us first examine the DIF response component as the function of frequency The plots from all three turns clearly reveal the presence of different frequency zones within which the local response assumes a particular character There are three such zones, only two can be discerned in the first turn plots since these do not go

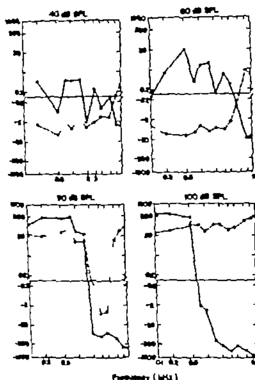


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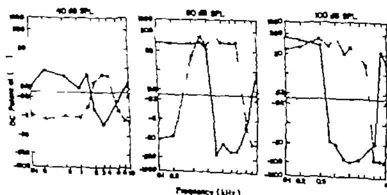


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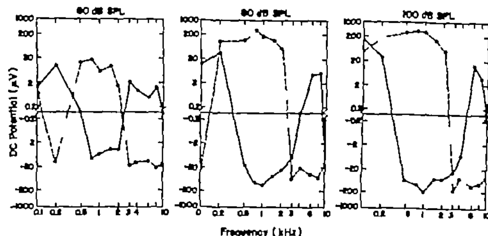


Fig 11 Median SP versus stimulus frequency functions at several signal intensities from the third cochlear turn. Plots are given for the DIF (●—●) and AVE (○—○) components.

data points to appropriately delineate the sharpness of the transition, moreover the median plots tend to blur sharp changes. In order to illustrate the actual situation, the 60 dB condition in turn two is plotted in Fig. 12 with much finer frequency divisions for one particular animal There we note that on the low frequency boundary the DIF response changes from +10 0 to −3 6 μV between 1 900 and 2 000 Hz, that is within 100 Hz.

The plots depicting the AVE response present a somewhat more complex picture than was seen for the DIF components. For the second and third turn responses three regions are again discriminable but in the first turn it appears that four frequency regions might be appropriately described In the higher turns in the vicinity of the best frequency of the electrode location, the AVE response component is positive. As with the negative DIF component here again a band whose width is dependent upon the signal strength is seen the more intense the stimulus, the wider the positive band about the best frequency Again the extension of the band with increasing intensity is primarily toward the lower frequencies. Above the positive AVE response region this potential turns negative, this of course cannot be seen in the first turn response since data are not shown for sufficiently high frequencies. Below the best frequency positive region the AVE response turns negative. In turns two and three this low frequency region

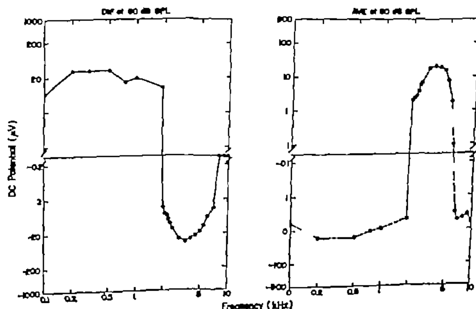


Fig 12 DIF and AVE SP components versus stimulus frequency functions for one representative animal, obtained from the second cochlear turn at a constant 60 dB SPL.

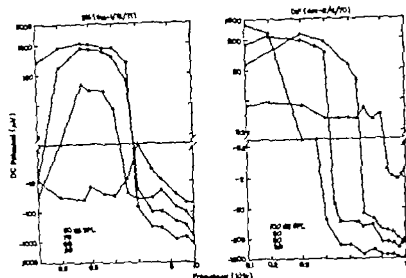


Fig. 13. Comparison between SP versus frequency functions obtained from scala media (SM) and the DIF component. Responses from the first cochlear turn are shown for representative individual animals. The parameter is sound pressure level.

of negativity is evident for only low and moderate signal levels because at high levels the positive region extends all the way down the measured frequency range. This negative region is also evident in the first turn AVE response, but here another complicating factor must be considered. Note that the negativity at low intensities extends down to 100 Hz, but as the intensity increases the response turns positive again. The higher the intensity the higher the frequency of this crossover. At 100 dB SPL the negative band is "filled in". It is probably worth emphasizing that the negative band is obliterated at high intensities by the simultaneous downward spread of the positive AVE component that is prominent in the best frequency region, and by the progressive upward spread of a low frequency positive region. This latter positivity is not evident in the higher turns, evidently a given frequency separation between the best frequency and its eliciting frequencies are required for the existence of this positivity.

Most of the plots presented thus far were obtained on the basis of median data. As a consequence the information contained in them represents the general trends seen in a fairly sizable number of animals. Individual animals depart from the general trend in the frequency and intensity regions where some component of the SP undergoes rapid changes. Since as we have seen complete polarity reversal can occur well within a 100 Hz frequency change (or for that matter within a 10 dB intensity change) it is not at all surprising that from animal to animal the exact crossover points do not remain at the same parameter values. It appears that even a slight difference in electrode location, to mention only one possible cause, could result in shifts of the crossover points between positive and negative SP components. The interaction of such individual differences is undoubtedly the cause of the jagged appearance of some of our median plots, particularly in the midfrequency and midintensity regions. For example in Fig. 4 (Turn-one input–output functions for DIF and AVE at 2 000 Hz) the average component vacillates rather sharply between 70 and 100 dB. This is clearly due to the differing crossover points among the animals that comprise the experimental sample.

The variety of plots shown above provide a quantitative description of the dependence of the SP as recorded in the perilymphatic scalae, upon the pertinent stimulus parameters frequency and intensity. Because of our limited access to the cochlea the recordings are made from only three locations that correspond to the three lower turns of the inner ear. On the basis

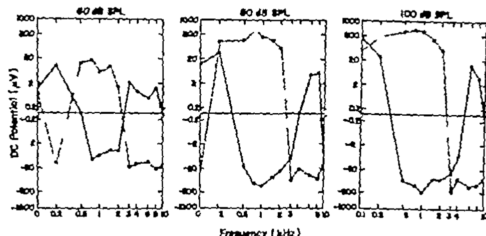


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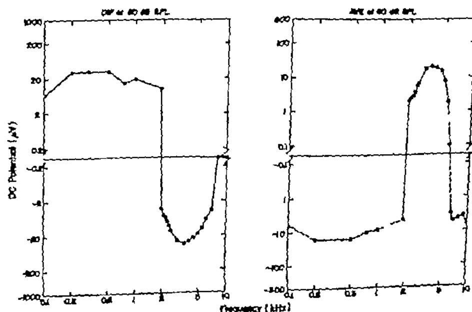


Fig 12 DIF and AVE SP components versus stimulus frequency functions for one representative animal, obtained from the second cochlear turn at a constant 60 dB SPL.

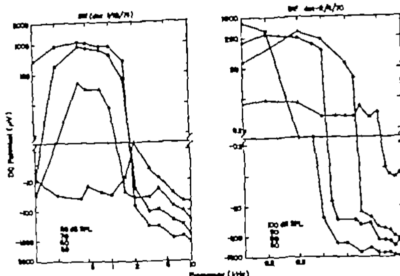


Fig 13 Comparison between SP versus frequency functions obtained from scala media (SM) and the DIF component. Responses from the first cochlear turn are shown for representative individual animals. The parameter is sound pressure level.

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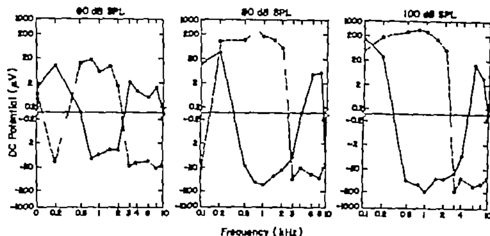


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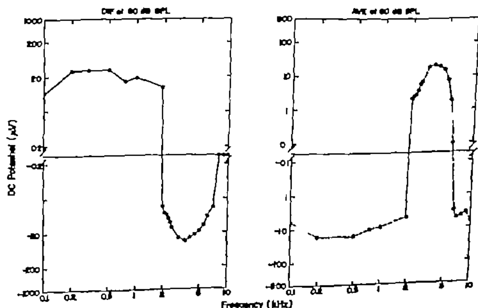


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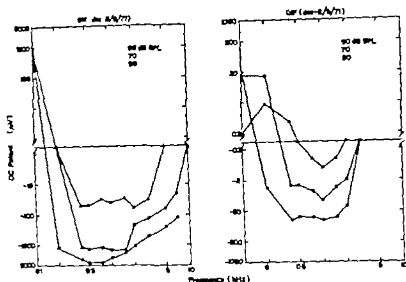


Fig 15 Comparison between SP versus frequency functions obtained from scala media (SM) and for the DIF component. Responses from the third cochlear turn are shown for representative individual animals. The parameter is sound pressure level.

We have commented before that the general increase in the width of the negative band with signal strength in the DIF recording takes place toward the lower frequencies. We noted that characteristically the high frequency edges of the negative zones tend to coincide at most signal levels. This is clearly not the case in the SM recordings where the spread of negativity is quite regular and pronounced. Probably the most important differences are seen at low sound levels. In turns one and two the SM potential stays negative even at low frequencies below approximately 50 dB SPL. This behavior is in marked contrast with the DIF pattern which showed unmistakable positivity below the best frequency region at any intensity level. This low-intensity SM negativity that can be seen at all frequencies has eluded previous observers. Two similarities between SM and DIF recordings that are probably worth emphasizing are the tendency for peak SP magnitudes to decrease toward the apex, and the similarity between the magnitudes of the maximal SP− and SP+ at a given location. The first observation can be illustrated by noting (at a given SPL) the magnitude of the maximum SP either positive or negative, in the various turns. The maxima in turn-one are generally in excess of the maxima from the other two turns. The second observation naturally applies to relatively high SPL conditions only. There one is impressed by the fact that SP+ can be the same order of magnitude as SP− provided one records at sufficiently low frequencies. This fact has not been emphasized in the past. It is then probably inappropriate to consider only the SP− whether obtained from SM or from the perilymphatic scalae as a dominant response. The SP+ can be equally as significant, only it is prevalent in a different frequency zone.

DYNAMIC PROPERTIES OF THE SP

The general statement is often made that the SP waveform reflects the shape of the stimulus envelope. This is true to some extent and under some conditions, but there are numerous complicating factors. It is known for example that the waveform in SM is very different from that in say SV (Johnstone & Johnstone, 1966; Honrubia & Ward, 1969), it has also been noted that in particular frequency and intensity regions the shape of the SP bears little resemblance to the stimulus envelope, primarily because during the time course of the stimulus the SP reverses polarity (Konishi & Yasuno 1963), a further obvious complication is the presence of the AP which obscures the onset of the response, and

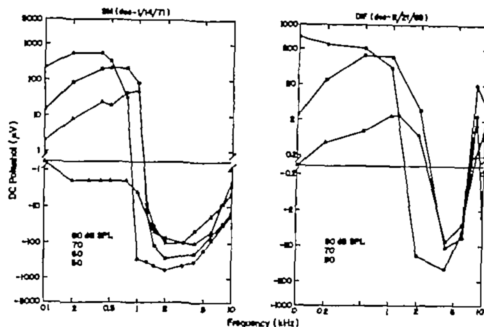


Fig 14 Comparison between SP versus frequency functions obtained from scala media (SM) and for the DIF component Responses from the second cochlear turn are shown for representative individual animals. The parameter is sound pressure level.

of the plots a number of conclusions have been drawn about the influence of stimulus parameters and recording location on the dc potential To investigate the relationship between SP in the perilymphatic scalae and that in SM we have repeated some of Honrubia & Ward s experiments We did this to assure similarity of procedure and overlapping parameter values, as well as to obtain data from the SM at low SPLs. Since Honrubia & Ward utilized direct oscilloscopic recording of the SP (not separated from CM) their signal to-noise limitations precluded the reliable recording of small dc potentials. Our averaging technique of course permits us to recover very small dc potentials from a high background of CM and physiological noise Moreover the procedure of evaluating the SP is different Honrubia & Ward measure the distance between the baseline and the center of the CM trace while we remove all ac components with the averaging process Thus the two sets of data can be expected to differ from one another

In Figs. 13 14 and 15 some of our SM recordings are presented These plots are for representative individual animals, for turns one two and three The graphs give the SP magnitude as the function of stimulus frequency with intensity as the parameter In each figure we have included for the sake of comparison the DIF–SP vs frequency plots of an individual animal The animal whose data are shown was chosen to be representative of our sample The only important difference between the two panels in a given figure is the ordinate scale Note that the logarithmic ordinate extends to $\pm 5\,000$ µV for the SM plots but only to the usual $\pm 1\,000$ µV for the DIF plots.

Even cursory inspection reveals that there is a great deal of similarity between the SM and the DIF plots. The most important feature of both, at least at high intensities, is the positive-to-negative transition with increasing frequency the pronounced negative zone around the best frequency and the diminishing response above the negative zone These overall details are quite familiar by now further discussion of them is not too profitable The consideration of some subtle differences between the SM and DIF plots, however is rather instructive

The width of the characteristic negative band is generally greater in the SM plots. This widening occurs without a very significant shift in the frequency of maximum negativity in other words the negative zone extends further toward both lower and higher frequencies. The extension, however is more pronounced and noticeable in the high frequency region, particularly as one observes the change in pattern with intensity

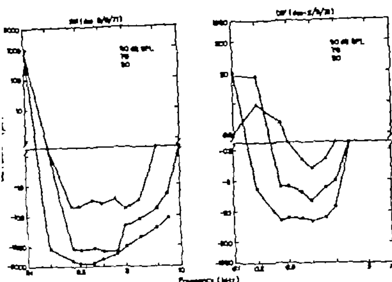


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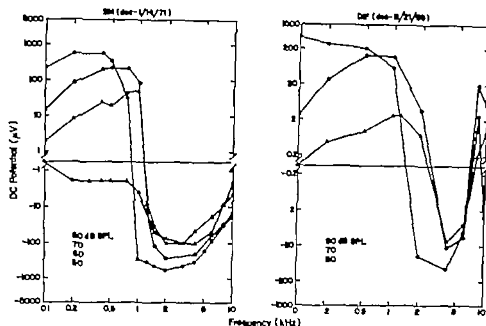


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the presence of the afterpotential that confounds the cessation of the response (Stopp, 1969). The purpose of this section is to provide some general observation on the SP waveform for a variety of stimulus and recording conditions.

In Fig. 16 a series of averaged SP traces are given as recorded from the first cochlear turn of one particular animal with differential electrodes. Both the DIF and AVE components are shown in the two panels of the figure, in any given horizontal row the stimulus SPL is constant and frequency is changing, while in any column the frequency is constant and intensity is the variable. The data were actually collected by sweeping across frequency at a constant SPL level. Aside from the different dynamic properties of the DIF and AVE SP components, these traces in Fig. 16 reveal some other interesting differences between the two responses. The expected difference is of course their selective sensitivity to AP and CM. The onset whole nerve AP response (usually N_1 and N_2) is clearly visible in most AVE traces, and it is particularly evident at the higher stimulus frequencies. In a certain frequency region in addition to the onset AP a cessation response is also seen in the AVE traces (Kupperman, 1970). The AP responses are almost completely invisible in the DIF plots. In the latter however there are some components that are absent in the AVE traces. Specifically there is some CM response that is due to a combination of ringing in the acoustic system and onset transient, which does not average out as does the ordinary CM response to the carrier sinusoid. This CM is evident at the beginning of the response and immediately after the cessation of the stimulus. It is manifested as relatively slow oscillations. These are best seen at high frequencies and high intensities, they are present only in the DIF trace. A third interesting, not SP related, difference between DIF and AVE responses pertains to their differing registration of the slow afterpotential (Teas et al., 1962; Stopp, 1969).

Let us first see the change in the DIF waveform at high intensities as frequency is varied. Not SP-related events are ignored now, that is the evident changes in ringing-response, and afterpotential are not being commented upon. At the lowest frequencies the DIF SP is clearly positive. At 500 Hz and 100 dB the waveform changes in that its later half begins to drop toward negative values. By 1 000 Hz the transition is complete and the final portion of the response is negative, above this the entire SP is negative, and it remains so for all higher frequencies. The waveform for all these high frequency high intensity DIF responses is quite square-shaped; these are the classically recorded SP^- components. The appearance of all AVE responses at 100 dB SPL is quite uniform, these are all positive and quite square-shaped. The traces are more interesting at 90 dB SPL. The DIF component could be described exactly as we have done above with the exception that the positive-to-negative transition occurs at a higher frequency, between 1 000 and 2 000 Hz. The AVE response encounters a double polarity reversal across frequency, the first between 1 500 and 2 000, the second between 4 000 and 5 000 Hz. Neither of these reversals is characterized by a peculiar waveform change. The description of the 80 dB DIF traces is similar to the one given for the two higher intensities, the only exception is the shift in polarity reversal to the region of 3 000 Hz. The high frequency transition back to positive polarity occurs at 6 000 Hz, without any obvious change in waveform. The next three intensity levels for which traces are shown are 70, 60 and 50 dB SPL. The DIF response at low frequencies is very small, generally positive, at these levels. The high frequency transition to negative polarity occurs between 4 000 and 6 000 Hz for all three, the emergence of the transition is first reflected by the later portion of the SP waveform. The AVE component is negative at low frequencies at the lower levels of stimulation, it turns positive between 9 000 and 10 000 Hz. It is interesting to note that at low intensities below approximately 1 000 Hz, where very little synchronized AP is evident, the waveform of the SP can be seen without the overlay of the neural response. In these conditions the AVE-SP appears to rise to its negative value relatively slowly

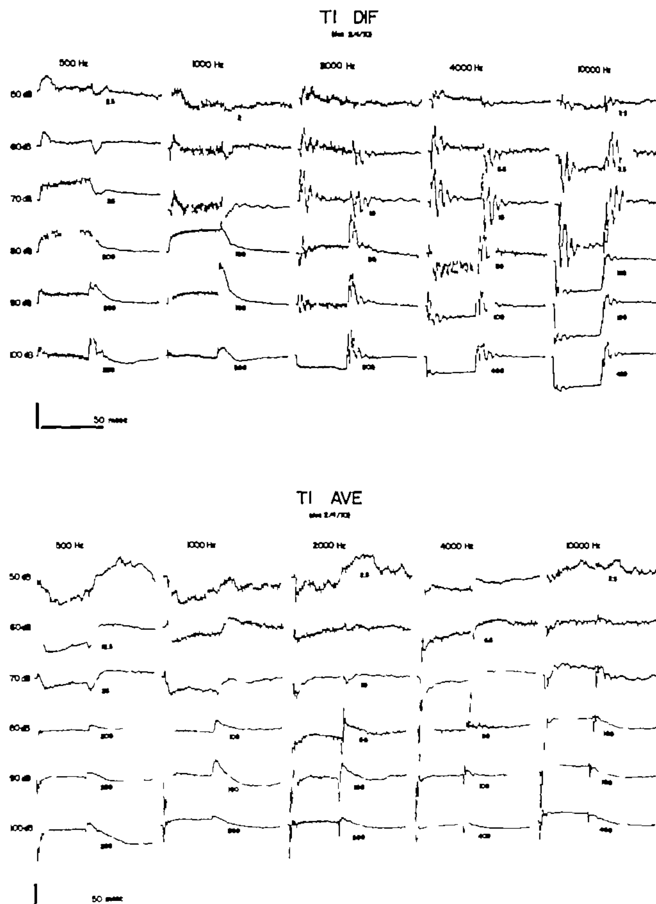
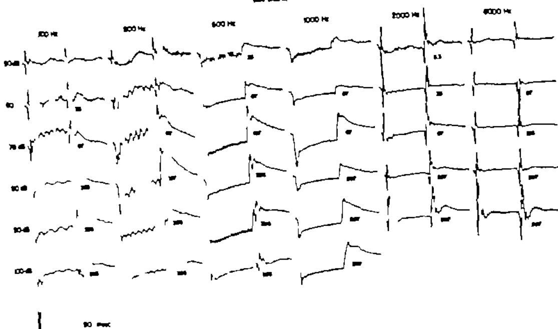


Fig 16 Averaged SP waveforms of the DIF and AVE components obtained from the first cochlear turn of one representative animal. In a given row the stimulus frequency is changing, while in a given column the stimulus intensity is changing. Stimulus duration is 40 msec, inter burst interval is 100 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.



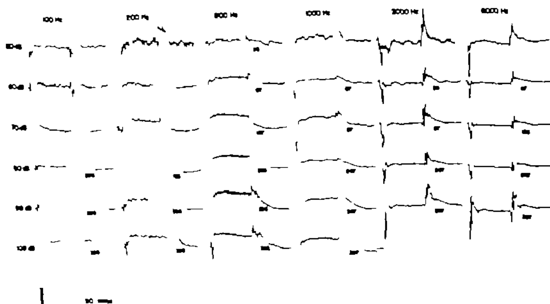


Fig. 18. Averaged SP waveforms of the DIF and AVE components obtained from the third cochlear turn of one representative animal. In a given row the stimulus frequency is changing, while in a given column the stimulus intensity is changing. Stimulus duration is 40 msec, inter burst interval is 100 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.

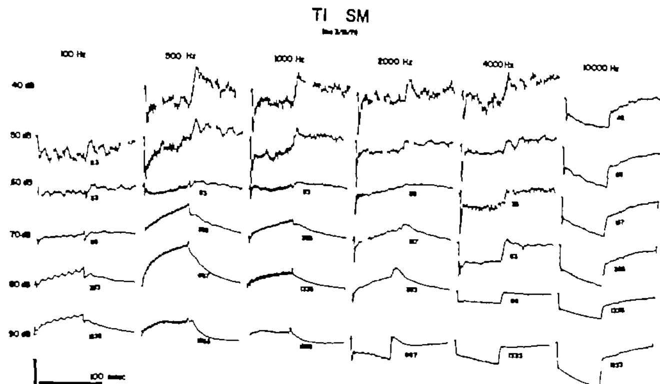
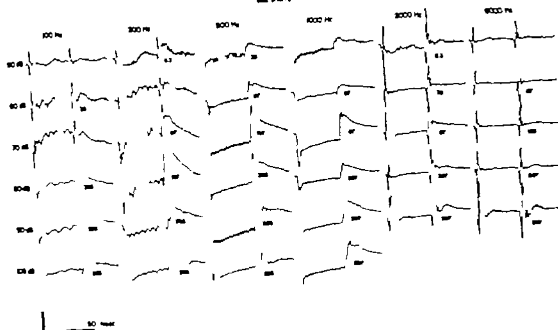


Fig 17 Averaged SP waveforms from the SM of the first cochlear turn of one representative animal. In a given row the stimulus frequency is changing, while in a given column the stimulus intensity is changing. Stimulus duration is between 60 and 80 msec and the interburst interval is 200 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.

In Fig. 17 a series of sample waveforms are shown for recordings from the scala media of the first cochlear turn. In analogy with Fig. 16 the responses are presented so that in any *horizontal row the stimulus intensity is constant* while in any vertical column the stimulus frequency is constant The entire array provides an overview of the frequency and intensity dependence of the SP from the SM of the first turn. The data were collected by keeping intensity constant and sweeping across frequency In the bottom row the high intensity 90 dB SPL, responses are depicted The SP is positive up to 1 000 Hz. The low frequency responses are slow potential changes, rapid components are notably absent Around 2 000 Hz the response is negative and reasonably square shaped As frequency increases the SP assumes its characteristic exponential form its magnitude increases during the duration of the signal This high frequency high intensity negative SP is actually composed of two response phases. Careful examination reveals that at both onset and cessation the smooth exponential change is preceded by a rapid response component The exponential portion begins considerably below the baseline, *most likely due to the presence of a rapid initial* SP response component The fast component is clearly seen at cessation. While the waveforms for the 80 dB condition are quite similar to the higher intensity pattern that was discussed above there are some important differences. The most striking difference is in the position of the polarity reversals and the attendant shifts in waveform. Compare for example the 2 000 Hz conditions at 80 and 90 dB While the response at 90 dB is negative and relatively square, it is positive at 80 dB and the waveform reveals the transitory nature of the SP As intensity is further lowered the negative-to-positive shift disappears and at 50 dB the response is negative at all frequencies At the lowest frequencies this negative response is quite square shaped there is a hint of a beginning transition between 500–2 000 Hz



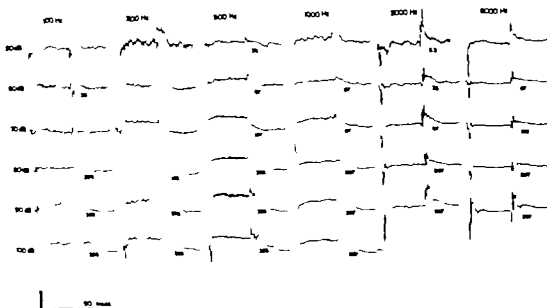


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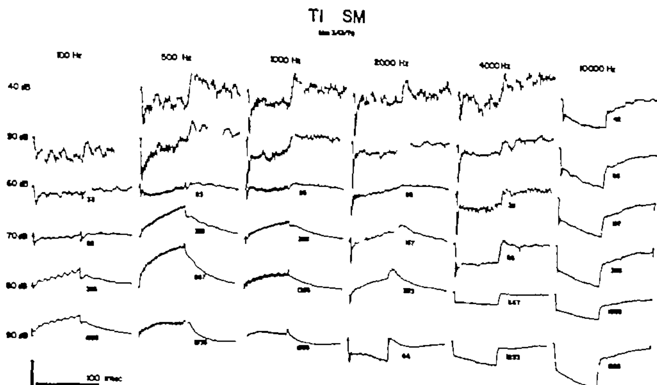
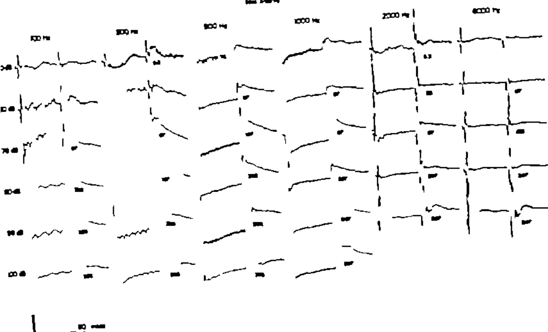


Fig 17 Averaged SP waveforms from the SM of the first cochlear turn of one representative animal. In a given row the *stimulus frequency* is changing, while in a given column the stimulus intensity is changing. Stimulus duration is between 60 and 80 msec and the interburst interval is 200 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.

In Fig. 17 a series of sample waveforms are shown for recordings from the scala media of the first cochlear turn In analogy with Fig. 16 the responses are presented so that in any horizontal row the stimulus intensity is constant while in any vertical column the stimulus frequency is constant The entire array provides an overview of the frequency and intensity dependence of the SP from the SM of the first turn. The data were collected by keeping intensity constant and sweeping across frequency In the bottom row the high intensity 90 dB SPL, responses are depicted The SP is positive up to 1 000 Hz. The low frequency responses are slow potential changes, rapid components are notably absent Around 2 000 Hz the response is negative and reasonably square shaped. As frequency increases the SP assumes its characteristic exponential form, its magnitude increases during the duration of the signal This high frequency high intensity negative SP is actually composed of two response phases. Careful examination reveals that at both onset and cessation the smooth exponential change is preceded by a rapid response component The exponential portion begins considerably below the baseline most likely due to the presence of a rapid initial SP response component The fast component is clearly seen at cessation. While the waveforms for the 80 dB condition are quite similar to the higher intensity pattern that was discussed above, there are some important differences. The most striking difference is in the position of the polarity reversals and the attendant shifts in waveform. Compare for example the 2 000 Hz conditions at 80 and 90 dB While the response at 90 dB is negative and relatively square, it is positive at 80 dB and the waveform reveals the transitory nature of the SP As intensity is further lowered the negative to-positive shift disappears and at 50 dB the response is negative at all frequencies. At the lowest frequencies this negative response is quite square shaped there is a hint of a beginning transition between 500–2 000 Hz



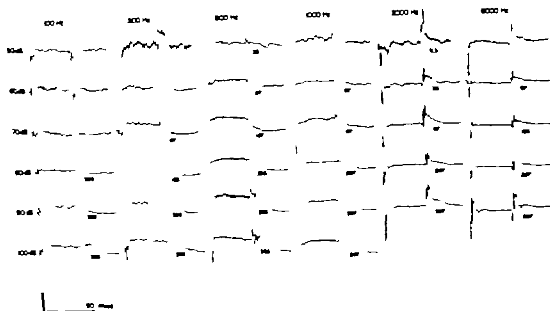


Fig. 18. Averaged SP waveforms of the DIF and AVE components obtained from the third cochlear turn of one representative normal. In given row the stimulus frequency is changing, while in given column the stimulus intensity is changing. Stimulus duration is 40 msec, inter burst interval is 100 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.

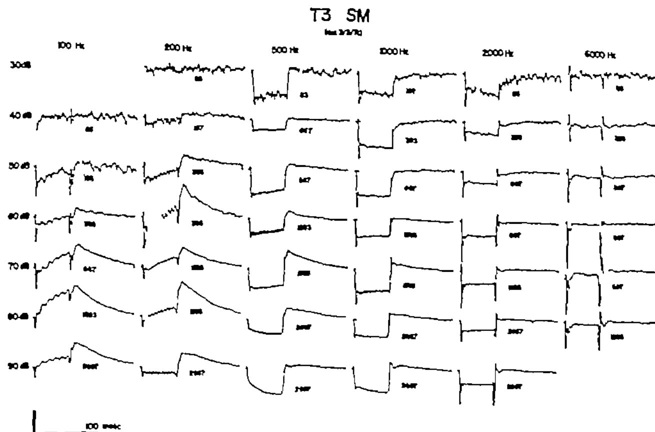


Fig 19 Averaged SP waveforms from the SM of the third cochlear turn of one representative animal. In a given row the stimulus frequency is changing, while in a given column the stimulus intensity is changing. Stimulus duration is approximately 60 msec and the interburst interval is 200 msec. The numbers next to the traces indicate the magnitude of the vertical calibration bar (in microvolts) that applies to the given trace. Positive potential is up in all traces.

in that the response seems to tend toward positive values, but the transition does not materialize and at the highest frequencies the waveforms have the already mentioned exponential, negative shape. It is instructive to remember the magnitude vs frequency functions plotted for turn-one SM data (Fig. 13) where we emphasized the loss of the positive low frequency response region at low intensities In the magnitude plot of Fig 13 the transitional zone where the response approached positive values was very clear it is interesting to note that this zone is also manifested in the appearance of the wave form as we have just noted

We will now consider the waveforms of SP responses from the more apical regions of the cochlea. Recordings from the third cochlear turn can serve as examples. DIF AVE, and SM responses are shown for representative animals, the first two sets in Fig. 18 while the latter set in Fig. 19 As before, in any given figure the stimulus intensity changes within a column and the frequency is variable within a row The low frequency DIF responses generally show a drift toward positive polarities during the onset of the response. This is quite clear for the 200 Hz low intensity conditions, where the SP starts out negative but turns positive by the end of the 40 msec ON-duration At higher stimulus levels for the 200 Hz, and at all levels at the 500 Hz condition the response stays negative during its entire duration, even though a pronounced decrease with time is seen. At increasing frequencies the responses become more square shaped and their magnitude is decreasing. Most AVE response waveforms are quite simple without characteristic transitions during the ON-period These responses are generally positive below 2 000 Hz, and negative at higher frequencies. As was seen in the first turn responses, the after

potentials show very interesting changes with stimulus parameter variations. As expected, the SM waveforms are considerably more complex than either the DIF or AVE ones. At the lowest stimulus levels the response, when discernible, is negative at all frequencies. We have emphasized this observation in connection with our first turn findings also. At 100 Hz the low level negativity gives way to a positive response as intensity is increased, the waveform however is quite complex in that the response rises and decays very slowly and that there are indications of fast onset and cessation transients superimposed on the slow wave. At 200 Hz the pattern is similar with the exception that at the highest SPL the response turns negative. It is worth noting here how this polarity reversal comes about. At this frequency one can clearly discern the presence of a fast response component at the onset and cessation of the response. This rapid component is in the negative direction but it is superimposed on a positive-going slow component. The net result of the superposition is that the overall response is positive between 60 and 80 dB, but that it turns negative at 90 dB. The responses are all negative in the best frequency region, that is for 500 and 1 000 Hz. At the highest intensities we see the familiar exponentially increasing SP at these frequencies. As in the first turn, the exponential changes are accompanied by the rapid on and off transients. Even at these frequencies there is an apparent remnant of the slow positive-going potential that we discussed in connection with the 200 Hz responses. The presence of this potential component can be discerned by considering the midintensity responses at 500 Hz. It is noticed that the response trace slants upward as time increases and that the baseline is approached slowly from above after the cessation of the stimulus. As intensity increases both of these effects decrease, first the actual response assumes its exponential shape, then the positive "afterpotential" diminishes. Actually if the 100 dB SPL condition would be shown here, the SP would approach the baseline very gradually from the negative direction. This waveform would strongly resemble the turn-one SM response at 10 kHz that was shown in Fig. 17. Above the best frequency region the third-turn SM waveforms are quite simple, there is apparently very little slow component in the response which is uniformly negative and gradually decreasing in size toward the higher intensities.

Discussion

The consideration that prompted this investigation was that a comprehensive study of an important class of cochlear phenomena, the summating potentials, was desirable but not available As we have indicated in the introduction, during the past twenty years a considerable amount of information has been produced on the subject, but very little quantitative data have emerged Particularly lacking was the description of the SP in all three cochlear scalae along the length of the basilar membrane for a wide variety of stimulus conditions. Our measurements of the potential gradient across the cochlear partition (DIF component) the common potential of the perilymphatic space at a given location (AVE component), and the potential inside the cochlear duct (SM component) were designed to provide a complete description of the dependence of these stimulus-related dc potentials upon stimulus parameters, and thus to pave the road toward the understanding of the *sources of origin and the significance of these* electrical events.

The most salient feature of the SP is seen to be its stringent dependence on stimulus parameters. At any given recording location in the cochlea the magnitude, the polarity and indeed the dynamic properties of the SP can easily be altered by moderate changes in stimulus frequency or intensity Thus a complete description of the SP phenomenon is necessarily complex particularly so considering our demonstration that the SP is not completely defined by the potential gradient across the cochlear partition but that another component (the AVE) is equally significant Clearly the customary reliance on the high frequency high intensity summating potential response from the basal turn as an indicator of the behavior of the entire phenomenon can provide only limited, one-dimensional information Thus the majority of investigations th assessed the dependence of the summati potential' upon a host of experimental alter tions of cochlear equilibrium (i e, pressu changes, anoxia, temperature, ionic balance, ha cell damage, etc) have actually described tl behavior of the negative DIF component Ou *results indicate that the positive DIF compone* or the positive AVE component can be just a significant as the much investigated negati DIF response, only a different set of stimuli and recording conditions are required for the elucidation It might be appropriate at th point to briefly summarize our observations o the effect of stimulus parameters upon th various recordable SP components.

At any given electrode location there is a nar row range of frequencies where the DIF com ponent is negative and the AVE component i positive at *all* stimulus levels. The combinatio of recording conditions that would provide th *best example of this situation would invol* basal turn electrodes and a stimulus frequency o 10 000 Hz. This combination would yield th cleanest example since only *local* activity would have to be considered, inasmuch as the high frequency stimulus would not spread mechanica excitation beyond the basal turn Both DIF and AVE input–output functions are relatively simple in this situation, they show proportiona increase (approximately unity slope) in potential with stimulus level The responses can be measured as low as 20 dB SPL, their magnitudes reach 700 1 000 μV at 100 dB At a recording location that is far proximal from the peak of the traveling wave envelope the DIF component is positive at all intensities except possibly at the highest levels where it tends to turn negative. A basal turn electrode location together with a 200 Hz stimulus would be the prototype for this

condition. We might wish to note here that careful examination of the input-output function suggests that there might be a difference in the rate of growth of the positive DIF potential at low levels as opposed to that at high SPLs. The breakpoint is around 60 dB below that the slope is shallower above that it is probably in excess of unity The AVE component exhibits a very characteristic pattern under these recording conditions. It is initially negative, passes through a maximum, turns positive between 60-70 dB and then continues to grow The change from negative to positive of the AVE response, and the break in the growth of the DIF response tend to occur at similar intensities. These changes can probably best be appreciated with the perusal of the raw SV and ST plots. For example in Fig 3, in the 200 Hz plot one can clearly see how the two potentials start to depart from a similar course at 60 dB signaling a change in the DIF and AVE components.

In the situation when the traveling wave maximum is far proximal from the recording electrodes we noted that the dominant potential is a relatively large negative AVE component The DIF response, when recordable, appears to be small in comparison with the AVE response and its input-output function tends to show unsystematic fluctuations. Under such conditions it is almost impossible to say with certainty whether or not the recorded DIF response is an artifact of inadequate cancellation of a common mode potential or if it is real but so small as to be impossible to assess reliably We tend to favor the first alternative The prototype condition for the demonstration of the negative AVE response is the one where recording takes place in the third cochlear turn and the stimulus is 10 000 Hz The AVE response can be recorded at very low stimulus levels, around 20-30 dB it grows at a rate of approximately 10 dB/20 dB (i.e. it is proportional to the square-root of the stimulus strength), and it achieves a magnitude of 100-200 μV at 100 dB SPL.

It is apparent that both DIF and AVE components of the SP can be positive or *negative* depending on recording location and stimulus parameters. It is the relative dominance of one or more of these constituent responses that determines the overall behavior of the SP under a given condition. The examples above were so chosen as to isolate the constituents in a relatively pure form. Clearly as we alter the stimulus frequency the output of our first turn electrodes will change from the relatively simple negative DIF component at high frequencies to the relatively simple positive DIF component at the lowest frequencies. In the midfrequencies the experimental situation is more complex and the influence of stimulus intensity and frequency is strongly felt. Similarly when the recording electrodes are in the third turn, their output can run the gamut from the very simple high frequency AVE response that is always negative, to the more complex low and midfrequency responses that are strongly intensity and frequency dependent. In those situations where the change in a stimulus parameter does result in the polarity reversal of one of the SP components, the transition from one polarity to the other is generally quite precipitous. In other words, a frequency shift of less than a hundred Hertz, or an intensity change of a few decibels can move the response from a large positive to an equally large negative value or vice versa. For those stimulus conditions where the response is relatively "simple" in other words where one polarity prevails with wide changes in one of the parameters (i.e. turn-one high frequency response is insensitive to intensity changes or turn-one very high intensity response is insensitive to frequency changes) the response variability from animal to animal is very small. In contrast in the transition regions the variability is quite high

The scala media response is similar in character to the DIF component but its magnitude is approximately ten times as large as the corresponding DIF component. The characteristic negative band at a given electrode location extends to a considerably wider frequency range in the scala media recording than in the DIF response. One interesting difference between DIF and SM potentials is that at very low intensity

levels the SM response is negative at all frequencies In other words even for frequencies that have traveling wave maxima far distally from the electrode location the SM response is negative provided the intensity is low enough. In this respect the SM response appears to be also related to the AVE component which as we recall is negative for comparable conditions.

The waveforms of the various response components also reflect the experimental conditions that produce them Thus the waveform of a relatively "simple SP component is quite uncomplicated examples might be high frequency DIF responses from the first turn, or high frequency AVE responses from the third turn These waveforms are relatively square and not influenced by stimulus level In contrast, the waveforms that are produced in the transition zones often change polarity during the duration of the stimulus, reflecting the complexity of the recording situation The waveforms of the scala media potentials are more complex in appearance because under most conditions they are composed of a fast and a slow component, and in addition they too are subject to the added complexity in the transition regions.

The presence of a variety of apparently distinct components in the overall SP response would tend to indicate that a multiplicity of sources could interact in producing this response Thus one could begin with the premise that the positive and negative AVE and DIF responses all originate from different sources, or one could even go beyond this and assume that apparent slope changes in the input–output functions of some of the components signal the shift of that component from one mechanism of origin to another Just by inspecting the data of course one cannot resolve the problem of identifying sources and mechanisms of generation. Experiments specifically designed to selectively influence some of the suspected sources are required to ascertain the true composition of the response. At this juncture we can merely venture a few plausible suggestions about the origin of the various SP components.

The first important problem concerns the independence of the AVE and DIF components Let us for example consider the relatively pure DIF and AVE responses that are seen from the basal turn at high frequencies. Here we can deal with phenomena that are related to a hydromechanical disturbance that is confined to the vicinity of the electrodes, thus it is unlikely that the electrical responses would be confounded by remotely located active sources. The question to be answered is are the AVE and DIF components the result of the operation of two independent mechanisms, or are they the manifestations of the same process. In the latter case one would have to assume that the potential gradient would be the primary response, it would originate in the organ of Corti in some asymmetrical distortion process, while the common potential would have to be construed as a resultant of the first potential and that it would be produced by a simple electrical asymmetry between the scala tympani and scala vestibuli Such asymmetry is actually suggested by the circuit model proposed by Johnstone et al (1966) it can be shown (Dallos, 1972) that linear resistance change in the element that simulates the organ of Corti resistance in that model does yield an asymmetrical potential change at the two nodes that simulate the scala vestibuli and tympani The result of this is a possibility for a common-mode potential to appear in the two scalae

Since a large fraction of this communication is devoted to the description of the properties of the AVE component, it is appropriate to consider in some detail how such a common-mode potential could be produced merely as the result of asymmetries in cochlear electroanatomy The DIF and AVE components as we have said reflect the voltage gradient across the cochlear partition and the common mode potential of the two perilymphatic scalae The question naturally arises whether or not an actual change in the potential gradient would in any way influence the AVE potential and conversely whether an actual common potential shift of the cochlear cross section (both scalae) would be at all reflected in the DIF component. The answer is that under "ideal" recording condi

tions the DIF and AVE components are independent from one another in other words if the recording situation is ideal then a change in the voltage gradient is manifested only in the DIF component, while a change in the common potential causes a change in only the AVE component. Ideal conditions mean perfectly balanced electrodes that are placed symmetrically across the cochlear partition, and whose amplifying chain possess the same gain. Such electrodes reflect the actual potential conditions in SV and ST without contributing their own bias. We must now emphasize a very crucial point While in the case of ideal recording one can be confident that DIF and AVE reflect the actual gradient and common mode potential, the transition to the concept that the gradient reflects potential sources within the cochlear partition (between the electrodes) exclusively and the common potential reflects remote or extra-partition sources exclusively is not a straightforward one An example will illuminate the problem. It has been the classic assumption (Tasaki et al 1954) that a potential source within the organ of Corti would be seen in opposite phase in SV and ST Thus Tasaki et al identified the source of CM to be located in the region of the reticular lamina and Konishi & Yasuno (1963) identified the source of SP in the same region on the basis of phase inversion and polarity reversal respectively when recording electrodes were thrust through this area Recent observations (Weiss et al 1969 Dallos et al., 1971) indicate that such phase reversals do not obtain under all recording conditions Specifically in regions of the cochlea where the electroanatomy is complex, that is where resistance or reactance patterns are asymmetrical or where there is sufficient crosstalk between adjacent turns or regions, the CM phase across the partition can depart quite significantly from 180° Such departures are also accompanied by magnitude differences. To explain this idea, let us expand the circuit diagram of Fig 2*a* in the form shown in Fig 2*b* Here we still have only one source of potentials, E_D, assumed to be within the cochlear partition between the electrodes The scala vestibuli and tympani recording points (V and T), however have asymmetrical resistance paths to the source and to the common reference The asymmetry is expressed by the multipliers k and n In this case the following relationships hold

$$\text{DIF} = E_V - E_T = \frac{(1+k)\,r E_D}{(1+k)\,r + (1+n)\,R},$$

$$\text{AVE} = (E_V + E_T)/2 = \frac{\tfrac{1}{2}(k-1)\,r E_D}{(1+k)\,r + (1+n)\,R}$$

It is quite clear that unless $k = 1$ both the AVE and DIF components are influenced by the source. When $k = 1$ the AVE component vanishes. The greater k becomes, the more the AVE component approaches the magnitude of the DIF component. It is interesting to note that the asymmetry of the resistance path between the source and the nodes does not influence the DIF and AVE components in a selective manner

A more general, even though still quite simplified, picture of the recording situation of interest can be studied with the aid of the circuit diagram shown in Fig. 2*c* This diagram is a refinement of Fig. 2*b* in it we assume the presence of two sources one (E) is a source within the organ of Corti between the electrode tips, the other (E_A) is a remote, possibly extra-partition source The two nodes, V and T represent the points of measurement in scala vestibuli and tympani. It is simply assumed that the resistance paths from the nodes to the sources and to the reference point are unequal The resistance differences are symbolized by the multipliers k m, and n In the desired optimal case the voltage difference between nodes V and T (DIF = E $- E_T$) would reflect E_D only while the *sum of* these voltages [AVE = (E + E)/2] would reflect E only It is a relatively straightforward matter to show that such conditions arise only if $k = m = n = 1$ Whenever there are asymmetries in the resistance paths, both E and E_A contribute *to both the* DIF and AVE measurements. The analysis of this circuit is straightforward The *solutions* for DIF and AVE voltages are given as follows.

levels the SM response is negative at all frequencies. In other words even for frequencies that have traveling wave maxima far distally from the electrode location the SM response is negative provided the intensity is low enough In this respect the SM response appears to be also related to the AVE component, which as we recall is negative for comparable conditions.

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The presence of a variety of apparently distinct components in the overall SP response would tend to indicate that a multiplicity of sources could interact in producing this response. Thus one could begin with the premise that the positive and negative AVE and DIF responses all originate from different sources or one could even go beyond this and assume that apparent slope changes in the input–output functions of some of the components signal the shift of that component from one mechanism of origin to another Just by inspecting the data of course one cannot resolve the problem of identifying sources and mechanisms of generation Experiments specifically designed to selectively influence some of the suspected sources are required to ascertain the true composition of the response. At this juncture we can merely venture a few plausible suggestions about the origin of the various SP components.

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hydrodynamic activity is confined to the basal region of the cochlea, thus we do not have to contend with remote potential sources. We remember that in this situation there is a sizable AVE SP component of positive polarity that coexist with the negative DIF component. The magnitude ratio between these two potentials is of the order of 3 to 5 the DIF component being larger These numbers are probably not significantly different from the predicted ratio. It is instructive to consider at this point the behavior of CM. In the situation that is of interest, namely when recording is in the basal turn and the stimulus is of high frequency all evidence at hand indicates that the CM has virtually identical magnitude and opposite phase in ST and SV (Dallos et al., 1971) We have obtained considerable amount of data to compare the relative magnitudes of CM and SP DIF and AVE components. One can simply state that in situations when the AVE CM component is 40–60 dB below the DIF CM component, the AVE and DIF SP components are of the same order of magnitude. In other words, the recordings indicate *virtually complete ac symmetry to go hand-in-hand with very significant dc asymmetry* The former is manifested by the fact that the common-mode CM potential is only a hundredth or a thousandth of the CM gradient. The latter is of course indicated by the fact that the AVE and DIF SP components are commensurable. There are two possible explanations for the difference between symmetry properties in the cochlea for ac and dc signals The first, and more obvious, explanation is that there are significant capacitive effects operating that would provide ac pathways between ST and SV and the potential source and also to ground, and would thus equalize the ac potentials without affecting dc imbalances The other explanation is that the circuit asymmetries are not significant and that one must seek the source of generation of the AVE component in other cochlear processes. There is no conclusive experimental evidence either for or against the presence of strong capacitive effects operating in the outer scalae of the cochlea. Some considerations, however drawn from the present experimental series, warn against accepting the presence of significant capacitive effects without actual experimental verification Consider that if it is indeed capacitive equalization of the CM that yields virtually identical ST and SV potentials at high frequencies in turn-one then one should be able to discern a gradual increase in CM disparity between these scalae as frequency is lowered and at very low frequencies the ST/SV microphonic ratio should approach that for SP The latter is of the order of 1.5–5 that is the ST potential is larger by that factor Even cursory study of CM versus frequency plots obtained from ST and SV reveals that there is a disparity between the potentials in the two scalae at low frequencies. The invariable result is, however that the CM is *larger* in SV than in ST below approximately 2 000 Hz. The disparity is of the order of 1.6:1 We have stated previously (Dallos et al 1971) that such differences (which are even more pronounced in the higher turns) are most likely the result of cross-talk between turns. It is thus possible that the circuit asymmetries are overshadowed by the opposite asymmetry provided by cross-conduction between turns This would, however require a very sizable amount of cross-conduction to completely reverse the effect. The resolution of this problem must await accurate reactance measurements in the cochlea. Lacking these, one cannot rule out the possibility that the AVE SP component is a manifestation of electroanatomical asymmetries of the inner ear

All SP components, being dc responses to an ac stimulus, are the products of nonlinear distortion. One of the central problems in dealing with the SP is the determination of the nature and site of the involved nonlinear processes. A fair number of mechanisms have been suggested by various investigators, these have been confined to yield explanation of what we now recognize as the DIF component, and more particularly the negative DIF potential. Davis (1957) assumed a one-way bending of the cilia that would result from a longitudinal relative displacement between the reticular lamina and the tectorial

$$\mathrm{DIF} = \frac{rE_D}{D}[k(m+1)r\varrho + (k+1)m\varrho^2] + \frac{rE_A}{D}[(n+1)(k-m)\varrho R]$$

$$\mathrm{AVE} = \frac{rE_D}{2D}[(k-1)m\varrho^2 + k(m-1)r\varrho] + \frac{rE_A}{2D}[k(n+1)(r+\varrho)R + k(m+1)r\varrho]$$

where

$$D = r[(m+1)kr\varrho + (k+1)m\varrho^2] + R(n+1)[kr + (r+\varrho)m\varrho].$$

There are a few obvious relationships between DIF AVE, E_D, and E_A that one can see by inspecting these formulae In the case when $k=m$ the DIF potential does not depend on E_A but it is completely determined by E_D. When $R=0$ the DIF potential is of course identical to E_D. In order for the AVE potential to be independent of E_D, it is necessary that both k and m be equal to unity Since we would like to construe the DIF component as being primarily reflective of the source E_D, and conversely the AVE component as representative of E_A, it would be desirable to know how good such representations are Error coefficients can be expressed in the following manner

$$e_{\mathrm{DIF}} = \frac{E_D - \mathrm{DIF}}{E_D} = 1 - \frac{\mathrm{DIF}}{E_D}$$

$$\text{and } e_{\mathrm{AVE}} = \frac{E_A - \mathrm{AVE}}{E_A} = 1 - \frac{\mathrm{AVE}}{E_A}$$

One can substitute the expressions for DIF and AVE that were obtained above and after that formulae for the error coefficients are obtained in the following form

$$e_{\mathrm{DIF}} = A + B\frac{E_A}{E_D} \quad \text{and } e_{\mathrm{AVE}} = F\frac{E_D}{E_A} + G$$

In these formulae A B F and G are all functions of r R, ϱ and k m n Notice that in the case when, for example $E_A=0$ the error in the DIF component is constant and it is determined by the asymmetry of the circuit. If however E is not zero then in addition to the constant error we have an error component that increases with E_A/E_D. This means that the error in the DIF component increases without bound when E_A becomes much larger than E_D. The converse is of course also true the error in the AVE measurement becomes larger and larger as the output of the E_D source exceeds that of the E_A source These relationships can be expressed by saying that the most accurate measurement of the DIF component can be obtained in situations when E_A is small compared with E_D. In the recording situation when E_D is small in comparison with E_A the DIF component is prone to severely misrepresent the former source The converse is true for the relation between AVE and E_A

We see that as the result of asymmetries in the electrical cochlear network one can obtain significant DIF and AVE components from both intra (E_D) and extra partition sources (E_A) Let us concern ourselves with estimating the expected AVE component when the only source is E_D, the generator within the organ of Corti The equivalent electrical circuit of the cochlear cross section with resistance values obtained by Johnstone et al (1966) as shown in Fig. 2*d*, is used to serve as the basis of the computations. The solution of this simple circuit problem yields the following relations $E_V = 0\,014E_D$ $E_T = -0\,05E_D$ $\mathrm{DIF} = 0\,064E_D$ and $\mathrm{AVE} = -0\,018E_D$. Clearly the circuit analysis predicts that the scala tympani voltage (E_T) is considerably in excess of the scala vestibuli potential, and as a consequence of this asymmetry there is a sizable AVE component. The computations moreover predict that the AVE component is of opposite polarity from the DIF component The ratio of the magnitudes of the predicted DIF and AVE components is 3 56 These computations indicate that there is a very real possibility that the AVE component that we measure in the stimulus-related DC response is a simple manifestation of the organ of Corti source produced by the asymmetry of the cochlear network. A good analogue of the above computation is the situation when recording is made from the basal turn with high frequency stimulation. In this case all

hydrodynamic activity is confined to the basal region of the cochlea, thus we do not have to contend with remote potential sources. We remember that in this situation there is a sizable AVE SP component of positive polarity that coexist with the negative DIF component. The magnitude ratio between there two potentials is of the order of 3 to 5 the DIF component being larger These numbers are probably not significantly different from the predicted ratio It is instructive to consider at this point the behavior of CM In the situation that is of interest, namely when recording is in the basal turn and the stimulus is of high frequency all evidence at hand indicates that the CM has virtually identical magnitude and opposite phase in ST and SV (Dallos et al., 1971) We have obtained considerable amount of data to compare the relative magnitudes of CM and SP DIF and AVE components. One can simply state that in situations when the AVE CM component is 40–60 dB below the DIF CM component, the AVE and DIF SP components are of the same order of magnitude. In other words, the recordings indicate *virtually complete ac symmetry to go hand-in-hand with very significant dc asymmetry* The former is manifested by the fact that the common-mode CM potential is only a hundredth or a thousandth of the CM gradient. The latter is of course indicated by the fact that the AVE and DIF SP components are commensurable. There are two possible explanations for the difference between symmetry properties in the cochlea for ac and dc signals The first, and more obvious, explanation is that there are significant capacitive effects operating that would provide ac pathways between ST and SV and the potential source and also to ground, and would thus equalize the ac potentials without affecting dc imbalances The other explanation is that the circuit asymmetries are not significant and that one must seek the source of generation of the AVE component in other cochlear processes. There is no conclusive experimental evidence either for or against the presence of strong capacitive effects operating in the outer scalae of the cochlea Some considerations, however drawn from the present experimental series, warn against accepting the presence of significant capacitive effects without actual experimental verification. Consider that if it is indeed capacitive equalization of the CM that yields virtually identical ST and SV potentials at high frequencies in turn-one, then one should be able to discern a gradual increase in CM disparity between these scalae as frequency is lowered and at very low frequencies the ST/SV microphonic ratio should approach that for SP The latter is of the order of 1.5–5 that is the ST potential is larger by that factor Even cursory study of CM versus frequency plots obtained from ST and SV reveals that there is a disparity between the potentials in the two scalae at low frequencies The invariable result is, however that the CM is *larger* in SV than in ST below approximately 2 000 Hz. The disparity is of the order of 1.6 1 We have stated previously (Dallos et al., 1971) that such differences (which are even more pronounced in the higher turns) are most likely the result of cross-talk between turns. It is thus possible that the circuit asymmetries are overshadowed by the opposite asymmetry provided by cross-conduction between turns. This would, however require a very sizable amount of cross-conduction to completely reverse the effect. The resolution of this problem must await accurate reactance measurements in the cochlea. Lacking these, one cannot rule out the possibility that the AVE SP component is a manifestation of electroanatomical asymmetries of the inner ear

All SP components, being dc responses to an ac stimulus, are the products of nonlinear distortion. One of the central problems in dealing with the SP is the determination of the nature and site of the involved nonlinear processes. A fair number of mechanisms have been suggested by various investigators, these have been confined to yield explanation of what we now recognize as the DIF component, and more particularly the negative DIF potential. Davis (1957) assumed a one-way bending of the cilia that would result from a longitudinal relative displacement between the reticular lamina and the tectorial

$$\mathrm{DIF} = \frac{rE_D}{D}[k(m+1)r\varrho + (k+1)m\varrho^2] + \frac{rE_A}{D}[(n+1)(k-m)\varrho R]$$

$$\mathrm{AVE} = \frac{rE_D}{2D}[(k-1)m\varrho^2 + k(m-1)r\varrho] + \frac{rE_A}{2D}[k(n+1)(r+\varrho)R + k(m+1)r\varrho]$$

where

$$D = r[(m+1)kr\varrho + (k+1)m\varrho^2] + R(n+1)[kr + (r+\varrho)m\varrho]$$

There are a few obvious relationships between DIF AVE, E_D, and E_A that one can see by inspecting these formulae In the case when $k=m$ the DIF potential does not depend on E_A but it is completely determined by E_D. When $R=0$ the DIF potential is of course identical to E_D. In order for the AVE potential to be independent of E_D, it is necessary that both k and m be equal to unity Since we would like to construe the DIF component as being primarily reflective of the source E_D, and conversely the AVE component as representative of E_A it would be desirable to know how good such representations are Error coefficients can be expressed in the following manner

$$e_{\mathrm{DIF}} = \frac{E_D - \mathrm{DIF}}{E_D} = 1 - \frac{\mathrm{DIF}}{E_D}$$

$$\text{and } e_{\mathrm{AVE}} = \frac{E_A - \mathrm{AVE}}{E_A} = 1 - \frac{\mathrm{AVE}}{E_A}$$

One can substitute the expressions for DIF and AVE that were obtained above, and after that formulae for the error coefficients are obtained in the following form

$$e_{\mathrm{DIF}} = A + B\frac{E_A}{E_D} \quad \text{and } e_{\mathrm{AVE}} = F\frac{E_D}{E_A} + G$$

In these formulae A B F and G are all functions of r R ϱ and k m n Notice that in the case when for example $E_A=0$ the error in the DIF component is constant and it is determined by the asymmetry of the circuit. If however E_A is not zero then in addition to the constant error we have an error component that increases with E_A/E_D. This means that the error in the DIF component increases without bound when E_A becomes much larger than E_D. The converse is of course also true, the error in the AVE measurement becomes larger and larger as the output of the E_D source exceeds that of the E_A source. These relationships can be expressed by saying that the most accurate measurement of the DIF component can be obtained in situations when E_A is small compared with E_D. In the recording situation when E_D is small in comparison with E_A the DIF component is prone to severely misrepresent the former source The converse is true for the relation between AVE and E_A

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merely a remote response in analogy with the similarly recorded AP. Indeed, this potential can be recorded in all regions of the cochlea that are distant from the maximum of the traveling wave envelope for a given stimulus: the response is strikingly present even far apically from the region of strongest excitation, i.e. in a segment where there is no excitation at all. This potential thus could be the reflection of distant activity: a passively conducted response. While this is a plausible concept, if adopted one must reconcile with it a few possibly contrary observations. First, we noted that the slope of the AVE input–output function is one-half as opposed to the unity slope of the functions of those potentials whose remote reflection this AVE⁻ is supposed to be. Second, the relationship between the magnitudes of the AVE and the DIF components is such that the concept of assigning a mere remote response character to the AVE does not appear to be straightforward. To explain these ideas, in Fig. 20 simultaneously recorded first turn DIF and third turn AVE responses are shown at various intensity levels for four high frequencies, 6, 8, 10 and 12 kHz. Even the lowest of these frequencies generate a traveling wave that is completely extinguished far basally from the third turn electrode location. There are several interesting observations that can be made with the aid of these pairs of input–output functions. We note that indeed the slope of the AVE component is approximately one-half, and moreover the four AVE plots could virtually superimpose. In other words, over this 6 kHz frequency range the third turn AVE response does not materially change with frequency. Highly significant changes do occur in the magnitude of the DIF components, however. As frequency increases this response becomes larger in the first turn. The relative magnitudes of the two components at various frequencies are very revealing. Note that at 12 kHz the DIF component is larger except at the lowest intensity while in contrast at 6 kHz the AVE component is larger except at the highest intensity. If the AVE component would be a mere remote reflection of the DIF component then it is unlikely

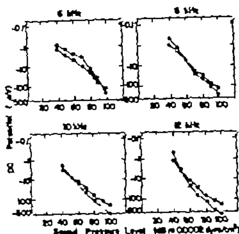


Fig. 20. Simultaneously recorded first turn DIF and third turn AVE SP responses from one guinea pig. Input–output functions are shown at four stimulus frequencies, 6, 8, 10 and 12 kHz. ●—● DIF ○—○ AVE.

that its magnitude would stay constant as the region of DIF-activity is constricted to ever diminishing segments in the basal portion of the cochlea (the frequency change corresponds to an approximately 2.5 mm movement of the traveling wave maximum). It would also be unlikely that its magnitude would be bigger than that of the DIF⁻ response that arises much closer to the point of maximum excitation such as in the 6 kHz case. If we assume, however, that the AVE component is not simply a conducted remote response, but the actual counterpart of the AVE component, then these difficulties are somewhat alleviated. The one remaining problem that we have no immediate explanation for is the peculiar slope of the AVE input–output function, namely one-half. In the narrow region where the AVE⁺ component is positive at all intensities (in other words in the region where this component is maximum) its input–output function possesses unity slope. The question why the potential drop in the source and sink regions (that is the AVE and AVE⁻ components) would increase at different rates, can probably be explained by the nonlinear spread of the region of excitation with increasing intensity and thus by a nonlinear growth of current density. The hypothesized longitudinal cur

membrane as the source of the SP⁻ Tonndorf (1970) proposed two hydrodynamic mechanisms that could yield asymmetrical responses. Johnstone & Johnstone (1966) presumed that the relation between hair bending and basilar membrane displacement is nonlinear Their model could account for both SP⁻ and SP⁺ Whitfield & Ross (1965) assumed that the basilar membrane displacement itself was asymmetrical Engebretson & Eldredge (1968) did not specify the site of the nonlinearity they only assumed that it is basically an asymmetrical saturating type one that can be expressed in terms of a polynomial transfer function Their analysis predicted close correlation between SP and other nonlinear cochlear processes, such as intermodulation distortion in the CM and the interference effect but could account for only the negative SP This scheme yielded an SP growth rate of 20 dB/10 dB SPL Our analysis of the electrical network model of cochlear electroanatomy that was proposed by Johnstone et al., (1966) clearly indicated that if it is assumed that linear displacements of the basilar membrane yield linear variations in the resistance of the organ of Corti then the resulting potential variations in the various scalae are distinctly nonlinear (Dallos, 1972) Others arrived at essentially similar conclusions (Strelioff 1971) The nonlinear CM potentials do have a dc component in this scheme, it is shown to rise with a slope of two with changing input intensity In studying cochlear distortion we have demonstrated that both harmonics and intermodulation components in the CM arise from a two-stage nonlinear process (Dallos et al 1969) At low sound levels the dominant nonlinearity is in the mechanoelectric conversion process of the hair cells, while at high sound levels a hydromechanical nonlinearity assumes dominance. It is reasonable to argue, based on the demonstration by Engebretson & Eldredge (1968) that there is a great deal of commonality among the various cochlear distortion processes, that at least some portion of the SP also might arise from the two major demonstrable nonlinearities hair cell transducer processes and hydrodynamic nonlinearities The demarcation between the two is probably controlled by t signal level It is then tempting to assume that t DIF SP response arises from the asymmetry the operating characteristic of the hair c transducer at low and moderate levels, and fro the rectification processes attendant to cochle hydrodynamics at high levels We have not some tendencies for two segments to exist in t input–output functions of the DIF componen with breakpoints at levels where the transitı between these two nonlinear processes usual occurs. It is quite probable that the source of t positive and negative DIF components is t same The difference between the two is th most likely the direction of shear on the cil is in different direction on the proximal (positi DIF) and distal (negative DIF) slopes of t traveling wave envelope. Békésy's (1953) obse vations on primary displacement directions c the two sides of the excitatory maximum suppo the possibility that inherently different she patterns might exist on the two slopes of th traveling wave envelope.

It is notable that the overall slopes of bot the DIF⁻ and DIF⁺ components input–outpu functions are approximately unity This is i contrast with the predictions that can be mad from the polynomial nonlinearity model c Engebretson & Eldredge or from the electro anatomy model that we have computed. Clearly the nonlinearity is more complex than wha these simple models envision.

While the tentative conclusion is that the posi tive and negative DIF components result fron the same nonlinear processes, the same migh be true for the two AVE components. One possibility is that a major portion of the AVE poten tials reflect voltage drops that result from longi tudinal current flow between strongly and weakly excited cochlear regions (Dallos et al., 1970) In this scheme the AVE⁺ potential would reflect the source region that would correspond to strong excitation, while AVE⁻ would be associated with the sink of the longitudinal current flow that is with areas of weak or nonexisting excitation. Cursory examination of the AVE component might suggest that this potential is

scala media than in the perilymph. From the presence of both slow and fast response components one can surmise that the electrode "sees" the scala media SP through a circuit involving both resistive and capacitive elements. Apparently such capacitance is not involved to any significant measure in the registration of SP from the two outer scalae.

Our final consideration is directed toward establishing some relationships between CM, SP and the traveling wave pattern. To facilitate the discussion in Fig. 21 we are presenting a composite graph based on data from one particular animal. Included in the graph are CM and SP recordings from the third turn of the cochlea. The CM magnitude (obtained with differential electrode recording) at a constant 50 dB SPL, the DIF and AVE SP components at constant 50 dB SPL, all as functions of stimulus frequency are compared with the schematic tuning curve of basilar membrane displacement for the cochlear location where the electrodes are situated (approximately 14.5 mm from the stapes). From Békésy's frequency map (1944) one obtains a best frequency of 400 Hz, and the tuning curve is constructed by assuming its basal slope to be 6 dB octave and its apical slope to be −100 dB/octave (Johnstone et al., 1970). We first note the good agreement between the frequency of the maximum CM and the maximum mechanical displacement. At the point of the maximum the phase of the CM is slightly in excess of 90° behind the sound, or what is equivalent, slightly more than 180° behind the CM in the basalmost part of the cochlea. In this particular case the maximum of the DIF response almost coincides with the maximum of the CM response; its frequency is about 300 Hz. It is striking that the DIF component peaks at a considerably higher frequency than the CM-traveling wave maximum. The difference is approximately one octave. This is a highly consistent finding. The AVE peak is more variable, in some animals it occurs at the same frequency as the DIF maximum, in others, as in the present case, it is at a lower frequency. The fact that the DIF component peaks at higher frequencies than the CM at a given location indicates that this potential has its maximum on the apical slope or even beyond the extent of the traveling wave envelope. We have shown that intermodulation components in the CM are similarly located with respect to the displacement pattern of the cochlear partition (Worthington & Dallos, 1971). These observations suggest that the nonlinearities that produce microphonic distortion at moderate sound levels and those responsible for the production of the DIF SP are related. It also appears that the positive DIF SP is best correlated with the point of maximum and the proximal slope of the traveling wave envelope, at least at low sound levels. As intensity increases, the negative DIF and positive AVE components expand much further basally and become the dominant responses over the entire spatial extent of the traveling wave.

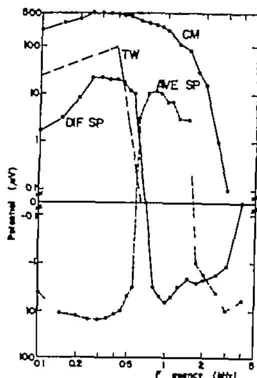


Fig 21 Various recordings obtained from third turn electrodes in one guinea pig. All these data are collected at a constant 50 dB SPL. The CM potential magnitude as recorded with differential electrodes is given in the top graph, the DIF and AVE SP components are also shown. The mechanical tuning curve (TW) for the cochlear location (14.5 mm) is schematized for comparison with the potential functions. The peak of the mechanical tuning curve is placed at 400 Hz in accordance with Békésy's cochlear map (1944) the low frequency slope is drawn as 6 dB/octave and the high frequency slope as −100 dB/octave

rent would be controlled by an active region in the vicinity of maximum excitation and it would flow into all inactive regions. This way the AVE⁺ would reflect the active region while AVE⁻ would prevail in all inactive regions Our study on cochlear damage (Dallos & Bredberg unpublished data 1970) indicated that there was excellent correlation between the integrity of the AVE⁺ producing active region and the normalcy of distant AVE potentials. For example in cases where there was almost complete damage of the third turn hair cell population and still a good first turn population existed the AVE potential recorded from the third turn in response to high frequency signals was virtually normal Conversely in this situation the low frequency low intensity negative segment of the first turn input-output function of the AVE potential was almost invariably missing One additional possibility that is worth mentioning is that some portion of the negative AVE response might reflect cochlear generator potentials In the original report on the SP phenomenon Davis and colleagues (1950) did assume that they were recording the post synaptic potential arising in the dendritic region of the auditory nerve A generator potential is certainly present in the auditory sense organ (Davis 1961) but it has not been experimentally identified as yet. It is possible that we do record this generator potential in those cases where at low signal intensity the AVE component is much greater than the DIF component, such as when recordings are made from the first turn at relatively low frequencies We have some preliminary evidence that indicates that these negative AVE potentials are indeed the manifestations of generator potentials. Thus for example these potentials disappear immediately after death while other SP components persist.

As we have noted there was a general similarity between SP patterns reflected by the DIF and SM components. Apparently both are primarily dependent on the potential gradient across the organ of Corti and are the manifestations of the same nonlinear processes. The differences between the DIF and SM patterns are probably attributable to the differing electrical circuit elements that are involved in the registration of these potentials at their respective recording sites One difference involved the wider spread of the SM component around its maximum. This is likely to reflect the better insulating properties of the cochlear duct than the perilymphatic channels The scala media is essentially a core conductor and potentials are expected to spread farther in it than in the more lossy scala vestibuli scala tympani complex Another related difference is the appearance of negative SP in the scala media at low intensities and at all frequencies. Apparently remote negative activity is conducted in the scala media with such small losses that it can overcome a generally small positive local response Finally the wave forms of the SP are radically different in the

scala media than in the perilymph. From the presence of both slow and fast response components one can surmise that the electrode "sees" the scala media SP through a circuit involving both resistive and capacitive elements. Apparently such capacitance is not involved to any significant measure in the registration of SP from the two outer scalae.

Our final consideration is directed toward establishing some relationships between CM, SP and the traveling wave pattern. To facilitate the discussion in Fig. 71 we are presenting a composite graph based on data from one particular animal. Included in the graph are CM and SP recordings from the third turn of the cochlea. The CM magnitude (obtained with differential electrode recording) at a constant 50 dB SPL, the DIF and AVE SP components at constant 50 dB SPL, all as functions of stimulus frequency are compared with the schematic tuning curve of basilar membrane displacement for the cochlear location where the electrodes are situated (approximately 14.5 mm from the stapes). From Békésy's frequency map (1944) one obtains a best frequency of 400 Hz, and the tuning curve is constructed by assuming its basal slope to be 6 dB octave and its apical slope to be 100 dB/octave (Johnstone et al 1970). We first note the good agreement between the frequency of the maximum CM and the maximum mechanical displacement. At the point of the maximum the phase of the CM is slightly in excess of 90° behind the sound, or what is equivalent, slightly more than 180° behind the CM in the basalmost part of the cochlea. In this particular case the maximum of the DIF+ response almost coincides with the maximum of the CM response. Its frequency is about 300 Hz. It is striking that the DIF component peaks at a considerably higher frequency than the CM-traveling wave maximum. The difference is approximately one octave. This is a highly consistent finding. The AVE peak is more variable, in some animals it occurs at the same frequency as the DIF maximum, in others, as in the present case, it is at a lower frequency. The fact that the DIF component peaks at higher frequencies than the CM at a given location indicates that this potential has its maximum on the apical slope or even beyond the extent of the traveling wave envelope. We have shown that intermodulation components in the CM are similarly located with respect to the displacement pattern of the cochlear partition (Worthington & Dallos, 1971). These observations suggest that the nonlinearities that produce microphonic distortion at moderate sound levels and those responsible for the production of the DIF SP are related. It also appears that the positive DIF SP is best correlated with the point of maximum and the proximal slope of the traveling wave envelope, at least at low sound levels. As intensity increases, the negative DIF and positive AVE components expand much further basally and become the dominant responses over the entire spatial extent of the traveling wave.

Summary

An extensive study was performed to delineate the dependence of the stimulus related dc poten tials of the cochlea (summating potential SP) on the parameters of the sound signal and on re cording location Potentials were obtained from all three scalae of the first three turns of guinea pig cochleas. Data are presented from all these electrode locations and in addition the potentials in the perilymphatic space are evaluated in terms of the potential gradient (DIF) across the cochlear partition and the common mode poten tial (AVE) of the two perilymphatic scalae at a given location. Information is provided in terms of SP magnitude versus stimulus intensity func tions with frequency as the parameter and also as SP magnitude versus frequency functions with intensity as the parameter Since a fairly large number of animals were used in this study and since consistent trends in the data were demonstrated, most results are given in terms of the median values of the available data. Aside from the SP magnitude data, representative SP waveforms are also shown for various stimulus conditions.

It was demonstrated that both SP magnitude and polarity as well as the waveform are very strongly dependent upon stimulus parameters and on the recording site This dependence however is orderly and predictable At a given recording location there is always a narrow fre quency band within which the response assumes a characteristic polarity Within the band the scala media and the DIF responses are negative and the AVE component is positive at any sound pressure level At frequencies below the characteristic region the DIF response is positive and the AVE response is negative at least at low and moderate stimulus levels. As intensity increases, the negative DIF and positive AVE responses become dominant at lower and lower frequencies, and at very high sound levels at frequencies up to a cutoff point the DIF negative and the AVE is positive. At frequenc above the characteristic band the AVE respon is negative at all stimulus levels, while the D component becomes negligibly small. The obtained from scala media is very similar in behavior to that of the DIF response, but mu larger in magnitude. Other differences inclu the observation that in contrast with the D component, the scala media response is negat at low sound levels even at low frequencies. T chararacteristic negative band is generally wi for the scala media SP than for the DIF co ponent.

Comparisons with cochlear microphonic da and with the known properties of cochlear tra eling waves (Békésy 1944 Johnstone et a 1970) indicate that the peak negativity in t DIF and scala media responses occurs appro mately one octave above the maximum of t traveling wave envelope and the maximum the microphonic magnitude Thus these respo ses are maximal on the falling slope and im mediately distal to the spatial extent of tl traveling wave In contrast, the positive DI component is more closely associated with tl proximal slope and maximum of the traveli wave envelope. The positive AVE compone peaks between the traveling wave maximu and the negative DIF component maximum The negative AVE response is prevalent both o the proximal slope of the traveling wave an beyond the actual existence of this wave.

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that the various components all uniquely depend on stimulus parameters, and that under appropriate conditions any of the components can become dominant. Another important result pertains to the description of the AVE component and the demonstration that a very significant common-mode potential contributes to the SP response and thus that the SP under most conditions is of the same polarity on the two sides of the cochlear partition.

Summary

An extensive study was performed to delineate the dependence of the stimulus-related dc potentials of the cochlea (summating potential SP) on the parameters of the sound signal and on recording location Potentials were obtained from all three scalae of the first three turns of guinea pig cochleas. Data are presented from all these electrode locations and in addition the potentials in the perilymphatic space are evaluated in terms of the potential gradient (DIF) across the cochlear partition and the common mode potential (AVE) of the two perilymphatic scalae at a given location Information is provided in terms of SP magnitude versus stimulus intensity functions with frequency as the parameter and also as SP magnitude versus frequency functions with intensity as the parameter Since a fairly large number of animals were used in this study and since consistent trends in the data were demonstrated most results are given in terms of the median values of the available data. Aside from the SP magnitude data, representative SP waveforms are also shown for various stimulus conditions

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Comparisons with cochlear microphonic data and with the known properties of cochlear traveling waves (Békésy 1944 Johnstone et al., 1970) indicate that the peak negativity in the DIF and scala media responses occurs approximately one octave above the maximum of the traveling wave envelope and the maximum of the microphonic magnitude Thus these responses are maximal on the falling slope and immediately distal to the spatial extent of the traveling wave. In contrast, the positive DIF component is more closely associated with the proximal slope and maximum of the traveling wave envelope. The positive AVE component peaks between the traveling wave maximum and the negative DIF component maximum The negative AVE response is prevalent both on the proximal slope of the traveling wave and beyond the actual existence of this wave.

Some preliminary hypotheses about the nature and origin of the various SP components are presented, but further work is required before firm statements can be made The important conclusions that arise from the present work indicate that the SP is a multi-component response,

that the various components all uniquely depend on stimulus parameters, and that under appropriate conditions any of the components can become dominant. Another important result pertains to the description of the AVE component and the demonstration that a very significant common-mode potential contributes to the SP response, and thus that the SP under most conditions is of the same polarity on the two sides of the cochlear partition.

Zusammenfassung

Eine umfassende Untersuchung wurde ausge führt um die Abhängigkeit der reizverbundenen de Potentiale der Schnecken (summierendes Potential SP) von den Parametern des Schallsignals und der Lage der Registratur zu beschreiben Potentiale von den drei Abstufungen der ersten drei Wendungen in Meerschweinchenschnecken wurden erlangt Gezeigt wurden Werte all dieser Elektrodenlagen und ausserdem sind die Poten tiale in dem perilymphatischen Raum berechnet in Form des potentiellen Ranges (DIF) über der Schneckenteilung und des gemein umstand Potentials (AVE) der zwei perilymphatischen Abstu fungen in einer gegebenen Lage Information wird herbeigeführt in der Form von SP Umfang gegenüber Reizintensitätfunktionen wo Fre quenz der Parameter ist und auch von SP Um fang gegenüber Frequenzfunktionen wo Inten sität der Parameter ist Da eine ziemliche Anzahl Tiere in dieser Untersuchung studiert wurde und da übereinstimmende Tendenzen in den Werten demonstriert wurden sind die meisten Resultate als Mittelwerte der verfügbaren Werte angegeben worden Ausser den SP Umfangswerten werden auch typische SP Wellenformen für verschiedene Reizverhältnisse gezeigt

Es wurde demonstriert dass SP Umfang und Polarität sowie die Wellen form sehr von Reiz parametern und der Lage der Registratur abhängen Allerdings ist diese Abhängigkeit regel mässig und voraussehbar In einer gegebenen Registraturlage gibt es immer ein schmales Fre quenzband worin das Verhalten eine charakter istische Polarität annimmt In dem Band sind die Abstufungsmedia und das DIF Verhalten nega tiv und der AVE Komponent ist bei jeder Laut druckhöhe positiv Bei Frequenzen unter der charakteristischen Region ist das DIF Verhalten positiv und das AVE Verhalten negativ jeden falls bei niedrigen und mässigen Reizhohen. Mit Zunahme der Intensität dominieren die nega tiven DIF und positiven AVE Verhalten bei niedrigen und niedrigeren Frequenzen und bei sehr hohen Reizhohen bei allen Frequenzen bis zur Unterbrechung ist die DIF negativ und die AVE positiv Bei Frequenzen über dem charak teristischen Band ist das AVE Verhalten bei allen Reizhöhen negativ während der DIF Komponent unbemerkenswert klein wird Die SP die von den Abstufungsmedia erhalten wurde, ist dem Benehmen des DIF Verhalten sehr ähnlich jedoch viel grösser im Umfang Andere Unterschiede schliessen die Beobachtung ein dass im Gegensatz zu dem Komponenten das Verhalten der Abstufungsmedia bei niedrigen Schallhöhen negativ ist sogar bei niedrigen Fre quenzen Das charakteristische negative Band ist im allgemeinen für die Abstufungsmedia SP weiter als für den DIF Komponenten

Vergleiche mit Schnecken mikrophonischen Data und mit den bekannten Eig nschaften der Schnecken wandernden Wellen (Bekesy 1944 Johnstone et al 1970) zeigen, dass die höchste Negativität in DIF und Abstufungsmedia Ver halten ungefähr eine Oktave über dem Maximum der wandernden Wellenhülle und dem Maximum der mikrophonischen Hohe passiert So sind diese Verhalten maximal auf der abfallenden Schräge und sofort distal zu dem räumlichen Ausmass der wandernden Welle Im Gegensatz ist der positiv DIF Komponent enger mit der proximal Schräge und dem Maximum der wan dernden Wellenhülle verbunden Der positive AVE Komponent gipfelt zwischen dem Maxi mum der wandernden Welle und dem des nega tiven DIF Komponenten Das negative AVE Verhalten überweigt sowohl auf der unmittel baren Schräge als auch auf der wandernden Welle und uber die Existenz der Welle hinaus.

Einige preliminäre Hypothesen über die Art

und den Ursprung mehrerer SP Komponenten sind gezeigt, aber ein weiteres Studium ist notwendig bevor eine bestimmte Darlegung gegeben werden kann. Die wichtigen Folgen die von diesem Studium hervorgehen zeigen, dass der SP ein Multikomponentverhalten ist, dass die verschiedenen Komponenten einzigartig von Reizparameters abhängen, und dass unter bestimmten Umständen jeder Komponent dominieren kann. Ein weiteres wichtiges Ergebnis betrifft die Beschreibung des AVE Komponenten und die Demonstration, dass ein sehr bedeutendes gemein-umstand Potential zu dem SP Verhalten beiträgt, und daher dass das SP Potential unter den meisten Umständen die gleiche Polarität auf den zwei Seiten der Schneckenunterteilung hat.

Acknowledgement

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SUPPLEMENT 304

Acoustic Middle Ear Reflexes

A Sensory-control System

BY

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Contents

This thesis is based mainly on experimental work presented in the following publications.

I BORG E. 1972. Excitability of the acoustic m stapedius and m tensor tympani reflexes in the nonanesthetized rabbit. *Acta Physiol Scand 85* 374

II BORG E. 1972 Regulation of middle ear sound transmission in the nonanesthetized rabbit. *Acta Physiol Scand 86* in press.

III BORG E. 1972. The dynamic properties of the acoustic middle ear reflex in nonanesthetized rabbits Quantitative aspects of a polysynaptic reflex system *Acta Physiol Scand 86* in press.

Reference to the above articles are indicated in the text by Roman numerals.

The aim of the present publication is

a) to review briefly current literature on middle ear muscle function and to point out some objectives for further investigation,

b) to discuss basic aspects of the use of frequency transfer functions in studies of reflex systems,

c) to present the main findings of the articles I II and III and to relate them to previous knowledge about middle ear muscle function and

d) to discuss specifically and generally the acoustic middle ear reflexes as a sensory-control mechanism in relation to the auditory system.

The following abbreviations are used

St m stapedius

TT m tensor tympani

OC olivocochlear

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Stockholm 1972

Introduction

A. CONTROL IN SENSORY SYSTEMS

1 General aspects.

Responses of sensory receptors and information flow in sensory nervous pathways are subjected to a variety of adjustments originating in, or mediated by the organism itself. In most sensory systems there are several efferent and feed-back control systems. Some have been extensively studied physiologically others are barely known to exist. Among the functionally studied control mechanisms the following can be mentioned the gamma-efferents to the muscle spindle, the external eye muscles, the pupil, the efferent nerve fibers to the cochlea, to the vestibular organ, to the lateral line organ and some descending nerve tracts controlling transmission in sensory relay stations.

The main concerns of the functional analysis have been the activation of the control systems and their influence on the impulse flow in the ascending sensory pathways. Some of these control systems, such as the pupil, have been regarded for the most part to function reflexively as feed-back mechanisms. Others have been found to mediate complex control signals which to a great extent are of central origin, e.g. the gamma motor system and the efferents to the lateral line organ (Russell, 1971). In general, sensory control mechanisms have been studied only in lower animals, since most of them have not been accessible to experiments in man. The mechanisms of the external eye muscles and the pupil of the eye, however have been investigated both in lower animals and in man. Recently the function of muscle spindles have been approached in human studies also (see e.g. Vallbo, 1971).

2 The auditory system.

In the auditory system of vertebrates a number of control mechanisms modify the ascending flow of information at different neural levels (for reviews, see Filogamo et al. 1967. Whitfield, 1968. Pfalz, 1969). Some of these systems have been established only anatomically (Held, 1893. Rasmussen, 1946, 1967. Borg, 1972 d) whereas others have been analysed functionally.

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A facilitatory influence is exerted by the superior olive on activity in the ipsilateral cochlear nucleus as has been shown electro-physiologically and pharmacologically by Whitfield and co-workers (for review see Whitfield, 1968). In a series of experiments, Pfaltz and others (for review see Pfalz, 1969) analysed the inhibitory influence on the response of cochlear nucleus neurons initiated by stimulation of the contralateral cochlea. This binaural interaction was suggested to play a rôle in directional hearing.

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In addition to these purely neural control mechanisms there are two others that act through striated muscles, (a) the movements of

the outer ear and (b) the contractions of the middle ear muscles, the m stapedius (St) and the m. tensor tympani (TT) The movements of the pinna have been found to have strong influence on the sound input to the cochlea in the bat (Wever & Vernon 1961) Recently the function of the pinna has been subjected to further analysis with respect to movements of the animal and the visual field (Schaefer et al., 1971) In the present study attention is focused on the other mechanical control system in the auditory periphery the middle ear muscles.

B MIDDLE EAR MUSCLES

1 General aspects

The two middle ear muscles, the St and the TT originate in the walls of the middle ear and insert on the ossicles. The St is innervated by the seventh cranial nerve and its contraction pulls the stapes in a posterior direction The TT is innervated by the fifth cranial nerve and its contraction pulls the eardrum medially The middle ear muscles are unique among the control mechanisms of the auditory system in as much as they are accessible for study in both animals and in man*) Quantitative information on the function of the middle ear muscle system in animals and/or in man can be gained from neuroanatomical, neurophysiological, behavioural and psychoacoustic experiments. It is reasonable to hope that such results can be combined successively to form a consistent conception about the function of the auditory input control in particular and the functional principles of sensory-control systems in general

Analysis of the middle ear muscle function gives rise to three main questions 1) What are adequate stimuli for muscle contractions? 2) To what extent is transmission of sound in the middle ear influenced by the muscles? and 3) What are the dynamic properties of this regulation?

*) Eventhough results were not obtained that could be ascribed to activity in the OC efferents, it now appears possible to also study the OC efferent functions in man (Picton et al 1971)

It is well established that nonacoustic as well as acoustic stimuli activate the middle ear muscles. Both in animals and in man the muscles contract during certain movements (Kato 1913 Carmel & Starr 1963 Salomon & Starr 1963 Simmons, 1964 a 1964 c *cf* Lüscher 1929) and during vocalization (Kato 1913 Carmel & Starr 1963 Simmons, 1964 a, 1964 c; Henson, 1965 Djupesland, 1967) Stimulation of the skin, especially on or near the outer ear and in the ear canal have also been shown to elicit contractions of the middle ear muscles (Kato, 1913 Klockhoff 1961) Quantitative information is lacking, however about the magnitude and consistency of the middle ear muscle activity evoked by these nonacoustic stimuli as well as the influence of the activity on sound transmission

2 Acoustic middle ear reflexes

Sound is the most consistently effective stimulus for middle ear muscle activation. The acoustic middle ear muscle reflexes have been recognized for nearly a century (Hensen 1878) yet their rôle in auditory perception is still far from well understood The reflex pathway as shown in studies on the rabbit (Borg, 1972 c) is basically a four neuron chain 1) primary auditory neuron 2) secondary neuron from the ventral cochlear nucleus to the medial superior olive, 3) interneuron to the facial motor nucleus (St) and the trigeminal motor nucleus (TT) 4) the motoneurons. In addition there is a shorter three-neuron pathway to the ipsilateral St as well as parallel multi-synaptic chains.

Sound having intensity well above hearing threshold and presented to one ear elicits contractions of the middle ear muscles in both ears In most animals both St and TT respond. In man whereas St is consistently activated as an acoustic reflex, TT contracts only as part of a startle reaction with acoustic or nonacoustic stimuli (Klockhoff 1961 Djupesland 1967) In a small percentage of individuals it is possible that TT contracts selectively in response to sound (Lidén et al 1970)

Several studies, both in man and animals,

have analyzed the functional properties of these muscles, chiefly with respect to excitability and influence on sound transmission in the middle ear Since the intensity and frequency characteristics of natural sound are rapidly varying functions of time, an analysis of the dynamic properties of the middle ear reflexes is, however essential for describing and understanding their rôle as regulators of the sound input to the inner ear

a Studies in man. The excitability of the middle ear muscles has been extensively investigated in man (for reviews, see Jepsen, 1963 Møller 1972), as well as the influence on sound transmission (Pichler & Bornschein, 1957 Neergaard et al 1963 Borg, 1968 Cancura, 1970) and the dynamic properties (Møller 1962 a Dallos, 1964 McRobert et al 1968 Tietze, 1969) Most experiments have been performed on nonanesthetized subjects by measurement of changes in the acoustic impedance of the ear (Metz, 1946 Møller 1961 Klockhoff 1961 Zwislocki, 1963) or as changes in the air pressure in the outer ear canal (Terkildsen, 1957 Weiss et al 1962 Holst et al 1963 Mendelson, 1966) In addition, a more direct measure of the muscle activity has been obtained from recordings of the electromyograms of the St and TT usually in connection to ear operations (Perlman & Case, 1939 Fisch & Schulthess, 1963 Salomon & Starr 1963 Djupesland, 1967) The regulation of sound transmission has been more difficult to determine Temporal bone preparations (Neergaard et al 1963 Cancura, 1970) have been used as well as subjects with temporary paralysis of the St (Borg, 1968)

In general, the results have shown that the St reflex threshold is about 80 dB above hearing threshold for pure tones (Jepsen, 1955 Møller 196_ b) and somewhat lower for noise (Møller 1962 a McRobert et al 1968 Flottorp et al 1971 Peterson & Lidén, 1972)

The influence on sound transmission in man is limited roughly to the frequency range below 2 0 kHz (Borg, 1968 Cancura, 1970) The sound is attenuated almost exclusively For low frequencies (below about 1 0 kHz), the attenuation increases at a fairly constant rate above reflex threshold a 1.0 dB increase of sound intensity at the eardrum is attenuated to about 0.3 dB (Borg, 1968). Small improvements of sound transmission have been observed for sound frequencies at 2 0 to 3 0 kHz (Cancura, 1970).

The dynamic properties of the St reflex are intensity dependent but available estimates show that the middle ear reflex open-loop transfer function in man has a cut-off frequency (point of 3 dB attenuation) of 2 to 4 Hz and that the closed-loop system has a resonance peak at about 5 Hz (Møller 1962 a).

The studies in man have been largely confined to a physiological analysis of the system and few psychoacoustic studies have analysed the rôle played by the middle ear reflexes in auditory perception (for a review see Loeb 1964)

In psychophysical experiments Smith (1943) and Reger (1960) showed that voluntary contractions of muscles in the middle ear increased hearing threshold for low frequency tones. The extent of these muscle contractions, both with regard to the number of muscles active (St, TT m tensor veli palatini Walsh, 1967) and the degree of activation, as well as their relation to the acoustic reflexes is, however unknown (Reger 1960)

In patients with clinical signs of unilateral Bell's palsy with St paralysis Jepsen (1955) found that the loudness of high intensity tones with frequency below 1 0 kHz was often higher in the ear with paralysed St than in the normal ear and the timbre was different Furthermore, a painful sensation associated with intense sound is commonly but not consistently found in persons with unilateral facial nerve damage and a presumed paralysis of the St (for a review see Jepsen, 1955 Hansen, 1965) Perception of sound at hearing threshold was found not to be changed during St paralysis (Jepsen, 1955) or in any case, it is not altered more than 5 dB

Patients with tendotomy of the St have been used to determine the rôle of St for speech discrimination in noise (Lidén et al., 1964), for

the outer ear and (b) the contractions of the middle ear muscles, the m stapedius (St) and the m. tensor tympani (TT) The movements of the pinna have been found to have strong influence on the sound input to the cochlea in the bat (Wever & Vernon, 1961) Recently the function of the pinna has been subjected to further analysis with respect to movements of the animal and the visual field (Schaefer et al. 1971) In the present study attention is focused on the other mechanical control system in the auditory periphery the middle ear muscles.

B MIDDLE EAR MUSCLES

1 General aspects

The two middle ear muscles, the St and the TT originate in the walls of the middle ear and insert on the ossicles. The St is innervated by the seventh cranial nerve and its contraction pulls the stapes in a posterior direction The TT is innervated by the fifth cranial nerve and its contraction pulls the eardrum medially The middle ear muscles are unique among the control mechanisms of the auditory system in as much as they are accessible for study in both animals and in man*) Quantitative information on the function of the middle ear muscle system in animals and/or in man can be gained from neuroanatomical neurophysiological, behavioural and psychoacoustic experiments. It is reasonable to hope that such results can be combined successively to form a consistent conception about the function of the auditory input control in particular and the functional principles of sensory-control systems in general

Analysis of the middle ear muscle function gives rise to three main questions 1) What are adequate stimuli for muscle contractions? 2) To what extent is transmission of sound in the middle ear influenced by the muscles? and 3) What are the dynamic properties of this regulation?

*) Eventhough results were not obtained that could be ascribed to activity in the OC efferents, it now appears possible to also study the OC efferent functions in man (Picton et al 1971)

It is well established that nonacoustic as well as acoustic stimuli activate the middle ear muscles. Both in animals and in man the muscles contract during certain movements (Kato, 1913 Carmel & Starr 1963 Salomon & Starr 1963 Simmons, 1964 a, 1964 c *cf* Lüscher 1929) and during vocalization (Kato, 1913 Carmel & Starr 1963 Simmons, 1964 a 1964 c, Henson, 1965 Djupesland, 1967) Stimulation of the skin, especially on or near the outer ear and in the ear canal have also been shown to elicit contractions of the middle ear muscles (Kato, 1913 Klockhoff, 1961) Quantitative information is lacking, however about the magnitude and consistency of the middle ear muscle activity evoked by these nonacoustic stimuli as well as the influence of the activity on sound transmission.

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tized animals have been presented. In most, chronically-implanted electrodes have been used to record cochlear potentials or the electromyogram of the middle ear muscles, chiefly in the cat and also in the bat and the guinea pig (Galambos & Rupert, 1959 Simmons, 1959 1960 a, 1960 b, 1963 1964 a, 1964 b, 1965 Carmel & Starr 1963 Baust & Berlucchi, 1964 Henson, 1965 Salomon 1966 Legouix & Foret, 1969). In a considerable proportion of these experiments the animals were restrained (Galambos & Rupert, 1959 Simmons, 1959 and others). The main concern of these studies has been the excitability of the reflexes, and the quantitative information on the regulation of sound transmission is sparse. The dynamic properties have only been studied on the basis of electromyograms (Salomon, 1966), which is of limited value for a description of the feed back function of the middle ear reflexes.

The most striking results of experiments with chronic-implanted electrodes were the low thresholds and variability of acoustic reflex responses, and the frequent nonacoustic activity of the muscles. The variability is to an important part related of fluctuation in state of wakefulness (Baust & Berlucchi, 1964), but other factors are also involved For example, reproducible reflex responses could only be obtained in cats after considerable effort, e g anesthetizing the animals after each experimental session (Simmons, 1964 b)

Furthermore, the variability has been probably due in part to difficulties in controlling stimulus conditions and in measuring sound pressure level In none of the studies in which chronic implants were used the sound pressure level was measured in the ear canal near the eardrum In some studies, foremost those where the animals were unrestrained, free-field stimulation was used (Galambos & Rupert, 1959 Carmel & Starr 1963 Starr 1964 Henson, 1965 Legouix & Foret, 1969) In this respect, it is well known that the pinna and the ear canal are important factors that influence the sound pressure level at the eardrum (Wiener & Ross, 1946 Worden et al 1964 Simmons & Beatty 1964 Wiener et al., 1965 Legouix & Foret, 1969)

The consequences of implanted electrodes in the middle ear have not been completely elucidated. It has not been shown that metallic implants are harmless to the function of the auditory periphery or the middle ear muscles (cf Simmons, 1967). To the contrary disturbances in middle ear muscle function seem probable: electrodes implanted in the St tendon of humans have been found to give rise to noise sensations (Salomon & Starr 1963). Influence of implants on excitable tissue of the ear are not unreasonable since it has been shown that metallic particles (e.g steel) implanted in the vitreous body of the eye dramatically influence the electrical activity of the retina (Knave, 1970). The effects on the electroretinogram were found to be dependent on the composition of the alloys used as implants. Electrodes implanted in the middle ear have been of steel as a rule but the composition has not been presented.

Thus, it appears desirable to investigate middle ear muscle function in nonanesthetized, unrestrained animals without the use of implants in the middle ear and with increased control of the stimulus conditions.

The use of different methods for studies of middle ear reflex function in man and animals serves to greatly complicate comparisons of data from animals and man. The higher reflex thresholds obtained by impedance measurements in man as compared to those obtained with chronically-implanted electrodes in cats have been attributed mainly to methodological shortcomings in the human experiments (Simmons, 1964 c). It would, indeed, have important consequences for our ideas about middle ear reflex function in man, and for further research, if the recent data from cats could be applied to humans in a quantitative way Methodological differences may be important, nontheless several differences between species have been revealed when identical methods have been applied to various animals, e g with respect to enzyme content of the middle ear muscles (Lotz et al., 1969), their response to succinyl-

temporary threshold shift after high intensity sound exposure (Mills & Lilly 1971) and for discrimination of double clicks (Wigand & Borucki, 1965) These authors have all reported differences between ears with and without St function.

One main difficulty with the forementioned psychoacoustic studies has been the determination of actual involvement of the middle ear muscles, e g the degree of St paralysis or voluntary activation The degree of St paralysis was in some experiments checked by recording the change, or lack of impedance change in the paralysed ear using contralateral sound stimulation in others only the involvement of the face muscles was observed It has been found in patients with Bell s palsy that the crossed response can be absent eventhough there is ipsilateral St activity on the affected side (Borg 1968 Borg unpublished) Thus, criteria used for St paralysis based on contralateral activation do not always suffice to exclude St activity in the ear used for psychoacoustic measurements Such shortcomings might account for some of the variability found

b Studies in animals Human experiments are necessary for psychoacoustic evaluation yet they are less well suited or even unacceptable for analysis of certain aspects of middle ear muscle function. Animal experiments can furthermore, often be performed under more well controlled experimental conditions than similar experiments in man The magnitude and mechanisms of the regulation of sound transmission and the open loop dynamic properties are most easily studied in animals. Animal experiments are indispensable for the analysis of the neuroanatomical basis of the reflex and its relation to other control mechanisms in the auditory system. The possible rôle of the middle ear reflexes in preventing or modifying fatigue and permanent acoustic trauma to the inner ear is another topic where animal experiments are appropriate.

Animal experiments have dealt chiefly with the basic properties of reflex excitability and influence of the reflexes on sound transmission through the middle ear Certain studies have also been concerned with acoustic trauma (Kato 1913 Taruya, 1953 Simmons, 1960 a Hilding, 1961) and the central reflex mechanisms (Hammerschlag, 1899 1901 Carmel & Starr 1963 Salomon 1966 Borg, 1972 c)

The results presented concerning reflex excitability and the influence on sound transmission have given a quantitatively inconsistent picture of these features. Factors such as narcosis (Borg & Møller 1967) decerebration or decortication (Carmel, 1963 Carmel & Starr 1963 Baust & Berlucchi 1964 Salomon, 1966) can be assumed to have influenced the results of acute experiments to an unknown degree.

Furthermore, studies of the regulation of sound transmission have regularly been performed with the acoustic bulla open and mostly with contralateral sound as the reflex stimulus (e g Wiggers, 1937 Bornschein & Krejci, 1952, Wever & Vernon 1955 1961 Møller 1965 Wigand 1965 Price, 1966) Openings in the wall of the bulla have been found recently to change the acoustic properties of the middle ear (Møller 1965 Tonndorf & Khanna 1967 Guinan & Peake, 1967) and also the effects of the middle ear muscles (Borg, 1972 a) The attenuation of a low frequency tone (800 Hz) by the middle ear muscles was found to be greater when the bulla was open than under normal conditions. There is also experimental evidence showing that the crossed reflexes are less excitable than the ipsilateral reflexes (Møller 1961 Borg & Møller 1968) in nonanesthetized animals and man. The difference is increased by anesthesia (Borg & Møller 1967) Thus, there are a number of technical details that may influence the magnitude of the recorded reflex responses and attenuation of sound transmission in acute experiments

The problems associated with narcosis have been realized for a long time. Thus, investigation of middle ear muscle functions in nonanesthetized animals without openings in the bulla and under conditions of ipsilateral sound stimulation became of primary interest

During the last ten to fifteen years an increasing number of experiments on nonanesthe-

tized animals have been presented. In most, chronically-implanted electrodes have been used to record cochlear potentials or the electromyogram of the middle ear muscles, chiefly in the cat and also in the bat and the guinea pig (Galambos & Rupert, 1959 Simmons, 1959 1960 a, 1960 b, 1963 1964 a, 1964 b, 1965 Carmel & Starr 1963 Baust & Berlucchi, 1964 Henson, 1965 Salomon, 1966 Legouix & Foret, 1969). In a considerable proportion of these experiments the animals were restrained (Galambos & Rupert, 1959 Simmons, 1959 and others) The main concern of these studies has been the excitability of the reflexes, and the quantitative information on the regulation of sound transmission is sparse. The dynamic properties have only been studied on the basis of electromyograms (Salomon, 1966), which is of limited value for a description of the feed-back function of the middle ear reflexes.

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Analysis of the basic physiological properties of the acoustic middle ear reflexes in nonanesthetized unrestrained animals using methods identical to those used in man should provide a basis of evaluating results obtained with methods specific to animal experiments, *e.g* experiments on effects of brain lesions, on protection from auditory trauma and on the physiological basis for use of the middle ear reflexes in clinical diagnosis.

For further reviews of the literature on the properties and function of the middle ear muscles, see *e g* Kato, 1913 Wever & Lawrence, 1954 Jepsen 1955 1963 Wersäll 1958 Cancura *1970 Møller 1972.*

C SCOPE OF PRESENT STUDIES

In the previous review of current literature on the middle ear muscle physiology several problems appeared that demand further investigation *One important task is a more detailed* quantitative investigation of the basic physiologic properties of the St and TT reflexes to sound in nonanesthetized, unrestrained animals.

The present study was undertaken in an attempt to analyse the acoustic middle ear reflexes quantitatively under well defined stimulus conditions in nonanesthetized unrestrained animals with respect to their excitability (I) influence on sound transmission (II) and dynamic properties (III) Methods were chosen to allow direct comparisons with data obtained in experiments on humans and to have minimal and controllable influence on the auditory periphery The total reflex (St and TT in conjunction) as well as the isolated St and TT reflexes were investigated by means of ipsilateral and contralateral stimulation The experiments were performed on chinchilla rabbits, animals found to be patient making anesthesia and restraining unnecessary

Three implications of these investigations may be mentioned a) to extend knowledge of the acoustic input control system b) the possibility of assessing species differences and c) general aspects on sensory system control mechanisms

The results showed that the excitability of the reflexes is significantly lower in the rabbit than in man. The regulation of sound transmission is about equally efficient as in man, only extended to higher frequencies in the rabbit The dynamic properties could be described by second-order differential equations. It is *suggested on the basis of the results* obtained that the acoustic middle ear reflexes extend the dynamic range of the auditory system for intensity decrease making and add adaptation to the peripheral auditory system.

Notes on the methods

A RECORDING OF REFLEX RESPONSES (I II III)

The activity of the acoustic middle ear reflexes was recorded simultaneously in both ears as changes in the acoustic impedance of the ear at 800 Hz. A total of 78 rabbits of the small *chinchilla strain* were investigated The animals *were sitting quietly in a box, open at the top* and they were not restrained The measuring devices were hermetically sealed to the ear canals. Each of the two devices contained three electroacoustic transducers, one stimulus earphone one earphone for the 800 Hz measuring tone and one microphone. The measuring tone had an intensity at the eardrum of 65—70 dB

SPL (sound pressure level re. 0.0002 μb). The output of the microphone was balanced out electrically. Contractions of the middle ear muscles upset the balance and the resulting 800 Hz signal was recorded on a two-track tape recorder (Revox G36) together with a 7.4 kHz trigger signal synchronous with the stimulus. Analysis of the responses was performed at a later occasion from the signals which were rectified and lowpass-filtered (cut-off at 50 Hz, roll-off slope of 18 dB/octave) visualized on oscilloscope and recorded on film.

The amplitude of the signal representing the magnitude of the impedance change was measured at the end of the stimulus. These values were plotted as a function of sound pressure level after they had been converted to per cent of the maximal ipsilateral response of each ear. The stimulus-response curves described the steady-state properties of the reflex. Two curves for the ipsilateral, and two for the contralateral reflexes were obtained at each stimulus frequency. The stimuli were bursts of pure tones of 0.5 or 1.0 sec duration, the rise time to 90 per cent and the decay time to 10 per cent was in each case 2 msec. The frequencies 0.5, 1.45, 0, 4.0, 6.0, 8.0, 10.0 and 12.0 kHz were investigated in the intensity range from below reflex threshold to about 125 dB SPL. The sound pressures in the ear canal were measured in each experiment individually. This was accomplished with one of the transducers in the impedance measurement device which was connected to a probe terminating close to the eardrum. For the most part all of the frequencies were not investigated in each animal.

The total reflex (St and TT combined) was recorded in the first one to six experimental sessions on each animal. After surgical inactivation of one of the middle ear muscles, response of the remaining muscle was recorded. The properties of the isolated TT were obtained after paralysing the St. Since the St influences middle ear sound transmission, the properties of the isolated TT obtained were not identical to the TT properties under natural conditions, *i.e.* in conjunction with the St. The ipsilateral and the contralateral responses of the bilaterally isolated TT were found to differ only slightly (I), however. Thus, an adequate approximation to the properties of the TT under normal conditions was obtained from the crossed responses elicited by stimulation of the contralateral ear having both St and TT intact. In certain experiments, both muscles on one side were cut to make the study of the open-loop properties of the (contralateral) reflex possible.

The technique used for reflex recordings was originally developed for measurements on humans (Møller 1960, 1961) and was later shown applicable to nonanesthetized rabbits (Borg & Møller 1968). The method has been analysed with respect to validity and reliability. The steady-state amplitude of the impedance change was found to be proportional to the amplitude of the rectified, integrated EMG of the St (Borg, 1972 a) and thus can be assumed to be proportional to the contraction force of the muscle (Bigland & Lippold, 1954). The threshold for change in cochlear microphonics and in the impedance at 800 Hz was comparable to the threshold for the EMG of the St within 1 to 2 dB (Borg, 1972 a). The influence of the 800 Hz measuring tone was found to be neglible if it was kept below 75—80 dB SPL (Borg, 1972 b). The stability of the recordings during single experiments and the reproducibility from day to day was quantitatively analysed (Borg, 1972 b) by approximating a Gaussian distribution function to the stimulus-response curves of the reflex. The variability was found to be within a few dB: the standard deviation for the slope was 1.0 dB and for the position along the intensity axis it was 1.9 dB for reproducibility.

B. MEASUREMENT OF INFLUENCE ON SOUND TRANSMISSION (II)

Middle ear muscle contractions influence the sound transmission through the middle ear within certain ranges of frequency. The level of excitation in the cochlea to a certain stimulus will thus differ when the muscles are function-

choline (Gisselson et al., 1957) their activity during chloralose anesthesia (Wersäll, 1958) and the development of conditioned reflexes. Simmons et al (1959) reported successful results from attempts to condition the middle ear muscles in the cat to light, whereas a similar procedure failed in man (Bates et al 1970)

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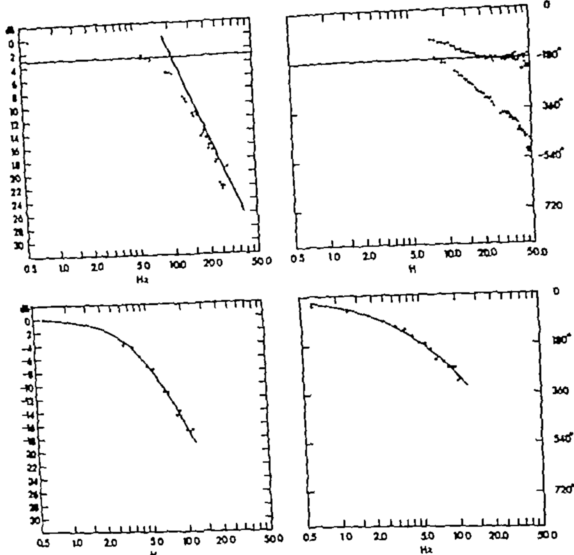


Fig. 1. *Left upper graph.* Amplitude characteristics of the open-loop total reflex calculated on the basis of differentiated step response. Dots show calculated values, dB re highest value. Logarithmic frequency scale. Continuous lines show 3 dB attenuation (horizontal) and asymptote of high frequency slope (−12 dB/octave). *Right upper graph.* Phase characteristics of the open-loop total reflex calculated on the basis of an impulse response. Dots show total phase shift and triangles show phase shift when phase shift due to latency had been subtracted. Latency was calculated on the basis of slope of high frequency phase response. Straight line shows —180 degree phase shift. *Lower graph.* Frequency transfer function (Bode plot) of the ipsilateral open-loop total middle ear reflex, based on the crossed response and correction for difference between ipsilateral and contralateral reflex. The approximated second-order system model frequency transfer function is shown by continuous lines.

of frequency transfer functions listed above, the frequency transfer function can be obtained by using any signal which covers the frequency range of interest. If the input signal contains all frequencies in equal proportion, *i.e.* it has a flat spectrum, the procedure is simplified. In such a case the frequency transfer function of the system is equal to the Fourier transform of the output signal. *Short impulses* are signals that have a flat spectrum and are often used to determine the dynamic properties of systems. The same is true for steplike stimuli, but in this case the response (step response) has to be differentiated first in order to yield the transfer function by Fourier transformation of the output.

A major advantage of frequency-domain an-

ing normally as compared to when they are in activated e g by surgery Thus, if it is possible to measure quantitatively the level of excitation in the cochlea in a sufficiently reproducible way one would be able to calculate the influence of muscle contraction by comparing the responses of the cochlea during normal activity of the muscles and for inactivated muscles. The middle ear muscles provide such a reproducible measure of the afferent activity originating in the cochlea (Borg, 1972 b) A comparison of stimulus response curves of the crossed reflex elicited from the ear under investigation, before and after inactivation of the middle ear muscles on the investigated side, show directly the influence of the muscles in terms of change in sound transmission to the cochlea

In the present experiments (II) as in a corresponding study in man (Borg, 1968) the crossed middle ear muscle reflex was used to measure changes of the afferent auditory activity The ipsilateral reflex in the ear with intact muscles was used as a reference since it was not influenced by the operation The shift in the curves was usually calculated on the basis of the average of stimulus-response curves obtained in several experimental sessions before and after inactivation of the middle ear muscles. The shift was a direct measure of the influence of the muscles on the transmission of the stimulus sound

C. ANALYSIS OF DYNAMIC PROPERTIES (III)

Dynamic analysis of control systems has been thoroughly treated elsewhere (see e g d Azzo & Houpis, 1966) and therefore only a few points will be discussed here.

The transfer function of a system is the ratio between the output and the input of the system This (complex) ratio is usually measured by sinusoidal excitation throughout a large frequency range. The frequency transfer function specifies the ratio of the amplitude of the output to the input (in dB) and the difference in phase for sinusoidal signal as a function of frequency over a wide frequency range. It is usually visualized as a Bode plot (Figs 1 and 3)

The usefulness of frequency transfer functions in dynamic analysis of biological systems is based mainly on three facts. First, the time course of any biological signal can be expressed as the sum of sinusoids of specified amplitudes and phase angles. The signal is thereby transformed from its original expression as a function of time (time-domain) to a function of the frequency of the sinusoidal components (frequency-domain) by means of a Fourier transform. Secondly each frequency component can be treated separately in a number of calculations Many times calculations are thereby greatly simplified Thirdly in any linear system the attenuation or amplification, and the shift in phase of each sinusoidal component of an input signal is independent of the other components present. Thus, if the frequency transfer function (the amplitude and phase characteristics) of a system is known, it can be used to determine the system output to an arbitrary input signal.

The dynamic properties of a system expressed as a frequency transfer function can thus be obtained by applying sinusoidal signals covering a wide frequency range to the system. Biological systems which are not linear can often be described similar to linear systems under certain restricted circumstances. Usually such systems behave like linear systems within small ranges of amplitude changes.

Frequency analysis with sinusoidal signals is the usual method for dynamic analysis of biological systems. However it is not suitable when the system is nonlinear in such a way that the onset differs from the decay properties as e g in the middle ear reflexes (II) In addition the recordings take considerable time if a high degree of frequency resolution and statistical stability of the spectral estimates are wanted If nonanesthetized unrestrained subjects are used it is especially important not to use too time-consuming methods.

However as follows from the basic properties

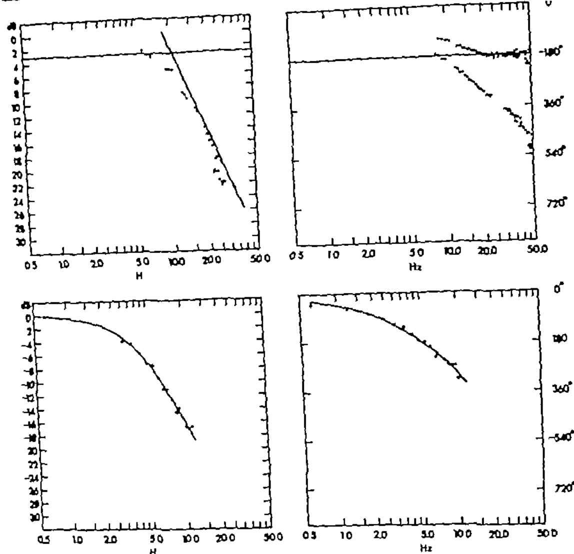


Fig. 1 Left upper graph. Amplitude characteristics of the open-loop total reflex calculated on the basis of differentiated step response. Dots show calculated values, dB re highest value. Logarithmic frequency scale. Continuous lines show 3 dB attenuation (horizontal) and asymptote of high frequency slope (—12 dB/octave). *Right upper graph.* Phase characteristics of the open-loop total reflex calculated on the basis of an impulse response. Dots show total phase shift and triangles show phase shift when phase shift due to latency had been subtracted. Latency was calculated on the basis of slope of high frequency phase response. Straight line shows —180 degree phase shift. *Lower graphs.* Frequency transfer function (Bode plot) of the ipsilateral open-loop total middle ear reflex, based on the crossed response and correction for difference between ipsilateral and contralateral reflex. The approximated second-order system model frequency transfer function is shown by continuous lines.

of frequency transfer functions listed above, the frequency transfer function can be obtained by using any signal which covers the frequency range of interest. If the input signal contains all frequencies in equal proportion, *i.e.* it has a flat spectrum, the procedure is simplified. In such a case, the frequency transfer function of the system is equal to the Fourier transform of the output signal. Short impulses are signals that have a flat spectrum and are often used to determine the dynamic properties of systems. The same is true for steplike stimuli, but in this case the response (step response) has to be *differentiated* first in order to yield the transfer function by Fourier transformation of the output.

A major advantage of frequency-domain an-

alysis is that the response of the system to any signal whose characteristics (amplitude in dB and phase as a function of frequency) is known can be determined easily by adding (dB-values) the signal characteristics to the frequency transfer function of the system. It is also simple to compensate for any filtering that may occur in the measuring and analysis apparatus

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The slope of the amplitude transfer function at high frequencies is a measure of the complexity of the system The number of integrations and differentiations that is made in the system can be estimated from this slope It is basic for determining the order of the differential equation which can model the dynamic properties of the system. Each integration adds —6 dB/octave to the slope of the high frequency skirt. The negative slope of 12 dB/octave as shown in Fig. 1 (upper left graph) thus implies that a second-order differential equation can be expected to describe the acoustic middle ear reflex system adequately

The phase transfer function shows the time lag of the different Fourier components in relation to the input (dots of Fig. 1 upper right) When the phase lag of the open loop system is 180° (+ n 360°) there is risk of oscillation in the system If the amplitude transfer function at this frequency is above 1 (0 dB) the system will oscillate with a continuously increasing amplitude (instability) Thus, it is important to know the characteristics of the system in this frequency region in order to predict its degree of stability

A certain amplitude characteristic implies a certain minimum phase change, *i.e* there is a minimal value for phase shift at each frequency If a system has a lowpass characteristic with a (negative) slope of 12 dB/octave, its minimum phase change is — 180° at high frequencies. In *a system with 18 dB/octave, the corresponding* minimum phase shift is — 270° In most biological systems there is a latency time that adds to the minimum phase shift. This additional phase shift is proportional to the frequency The dots of Fig. 1 (upper right graph) show the total phase shift of the middle ear reflex system The triangles show the phase shift after subtracting the phase shift due to latency

The latency can either be determined directly from the time function responses, or from the slope of the phase transfer function at high frequency Measurements in time-domain are uncertain for several reasons. Due to the gradual onset of the reflex response it is difficult to decide the point of departure from the baseline. Background noise adds variability and lag due to the filters used in the recording apparatus contributes to the latency In the present study latency was determined from phase curve. The value obtained thereby becomes based on information in the response curve as a whole and corrections for filtering effects are easy

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The dynamic properties of the middle ear reflex were found to be nonlinear with respect to amplitude. On the basis of earlier experiments (Borg, 1971 b) it was possible to derive conditions for which linear analysis methods could be used. It was concluded that the reflex functions as a different linear system for each reflex response amplitude. This assumption appears to be valid provided that the stimuli are rapidly changing in amplitude. During those circumstances, the reflex could be analysed using linear analysis methods. Furthermore, the onset and decay properties differed and therefore were analysed separately.

The technical details for determination of frequency transfer functions were presented in article III. Only a short summary is presented here. The signal representing the impedance change was sampled and converted to digital form in a computer (IBM 1800). The sampling started at the beginning of the stimulus as indicated by the trigger signal. The sampling rate (100 Hz) made it possible to determine the transfer function up to 50 Hz (Blackman & Tukey 1958).

The open-loop transfer functions were described by a mathematical model as a second-order system with transport delay. The parameters were determined by approximating the model transfer function to the values calculated from experimental recordings by using the least mean-square criterion for best fit. The parameters of the model were determined at several input amplitudes. The intensity dependence of the parameters was expressed by linear functions.

Outline of results

A. STEADY STATE PROPERTIES (I, II)

1. Excitability

The steady-state properties of the ipsilateral total middle ear muscle reflex in response to pure tone stimulation are summarized in Fig. _. The light shaded together with the heavily shaded area represent the region of tone frequency and sound pressure level for which response was obtained from the ipsilateral total middle ear reflex in awake, unrestrained rabbits. The threshold, defined as 10 % of the maximal obtainable impedance change, is indicated by the thin continuous line. The thin white line shows the threshold of the TT reflex when working together with the St, i.e. under normal conditions. The total reflex activity below this level consisted only of the St response. The difference in threshold between the St and TT reflexes was about 10 dB, independent of sound frequency. The excitability of the TT reflex was found to be influenced by the St activity particularly at low sound frequency. The isolated TT treshold (St cut) was on the average only 3 dB higher than the total reflex threshold at 0.5 kHz, but 10 dB at and above 2.0 kHz.

The average threshold for the ipsilateral total reflex and the St reflex was 98 dB SPL at 0.5 kHz and decreased by about 12 dB/octave to about 0 kHz. Above 4.0 kHz it was on the average 70 dB SPL. The lowest threshold value ever observed was 44 dB SPL (at 4.0 kHz). The

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quencies of stimulation it was found that the presence of oscillations in the reflex response amplitude was strongly correlated to attenuation of stimulus sound. It was thereby possible to judge from single responses if the stimulus sound was attenuated by the muscle contractions. A lack of oscillation did not, however exclude an attenuation of the stimulus. This procedure was utilized for frequencies between 4.0 kHz and 8.0 kHz since in this range responses did not regularly reach sufficient amplitude to influence the stimulus and thus to justify a laborious analysis based on stimulus-response curves. This shortcoming was due to limitation in the stimulus earphones.

It is interesting to note that the threshold for attenuation coincided with the reflex threshold only for the lowest frequency investigated 0.5 kHz (Fig. 2). At higher frequencies only responses well above threshold for impedance change at 800 Hz influenced sound transmission. The threshold for the influence on transmission was therefore nearly independent of frequency at 90—100 dB SPL. Improvement of sound transmission during middle ear muscle contraction was only occasionally observed and it had so small a value that it could not be differentiated from normal variability in a reliable manner.

In order to characterize the magnitude of the influence on sound transmission, the concept efficiency of regulation (or regulatory efficiency) was introduced (II). It was defined as the slope of the curve showing the relation between sound pressure level in dB (re. ipsilateral reflex threshold) and the attenuation of sound expressed in equivalent decrease in sound pressure level (re. stimulus sound pressure). Above threshold for attenuation the regulatory efficiency was about 0.7, i.e. 0.7 dB attenuation per 1.0 dB increase in sound pressure level in the ear canal (0.7 dB/dB). This value was nearly independent of the frequency of the stimulus tone and refers to closed-loop conditions, *i.e.* when the stimulus is attenuated by the muscles.

For a quantitative description, it is often more important to know the equivalent magnitude of attenuation when the stimulus is not itself influenced by the muscle contraction (open-loop). Such is the case when the middle ear muscles are inactivated in the stimulus ear or when a high frequency sound elicits a contraction which does not influence the sound itself (the light shaded of Fig. 2). Such a sound might attenuate a simultaneously present low frequency sound which has intensity below reflex threshold. The steady state open-loop efficiency of regulation was found to be about 2 dB per 1.0 dB increase above reflex threshold (2 dB/dB). This seems to indicate that a 2.0 kHz tone 10 dB above reflex threshold (not itself influenced by the contraction) would attenuate a simultaneously present 0.5 kHz tone below reflex threshold by 20 dB. This very high value could not be verified experimentally: the value calculated from the recordings was 5—10 dB. This discrepancy was probably due to the above-mentioned fact that the slope of the impedance-change stimulus-response curve was steeper at 0.5 kHz than at 2.0 kHz.

The attenuating efficiency expressed as "dB attenuation per per cent increase in impedance change" is probably more generally applicable but is still more complicated to express in simple mathematical terms. A numerical transformation can be made when stimulus-response curves for impedance change are available at the sound frequencies of interest.

The steady-state open-loop gain equals (K/ab in equation on page 14) was estimated to 4 corresponding to the open-loop efficiency of regulation 2 dB/dB.

The St was found to be the most important regulator of sound transmission. Above 2.0 kHz, only the St reflex contributed to the attenuation of the sound. At 0.5 kHz the TT provided about 0.2 dB (above its theshold) and the St about 0.5 dB of the total regulatory efficiency of 0.7 dB per 1.0 dB increase in sound pressure.

B. DYNAMIC PROPERTIES (I, II, III)

The temporal characteristics of the reflex activity was investigated in two steps. a) qualita

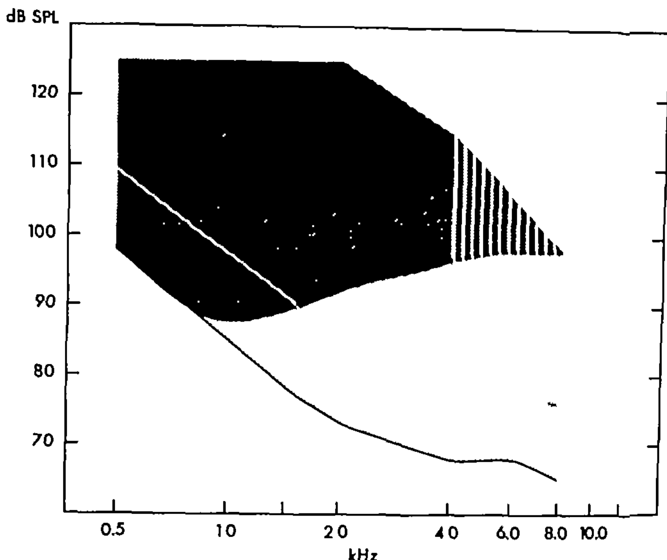


Fig 2 Static properties of acoustic middle ear reflex. Threshold of total reflex (St in conjunction with TT) is shown by the thin continuous line and it is identical to St threshold. Threshold of TT is shown by thin white line. Dark shaded area shows region where single pure tones are attenuated by the middle ear muscle contraction elicited by the pure tone itself (Copied from II)

individual variability was great. At 2.0 kHz the threshold covered nearly a 40 dB range. The reproducibility for individual rabbits was, however good (Borg, 1972 b)

The dynamic range was arbitrarily defined as the range (in dB) between the sound levels that resulted in a response amplitude between 10 and 80 % of the maximum obtainable impedance change. It was observed to be dependent on sound frequency. This range was smaller at low frequencies (15 dB at 0.5 kHz, total reflex) than at high frequencies (28 dB at 4.0 kHz). The isolated ipsilateral St reflex did not differ from the total reflex with respect to dynamic range and shape of the stimulus response curve. On the other hand the TT reflex (when in conjunction with the St reflex) had a less steep stimulus-response curve especially at low frequency and this curve did not regularly reach 80 % (of its maximum when isolated) within the intensity range available

2 *Regulation of sound transmission (II)*

The thick continuous line in Fig 2 shows the lowest sound level for which attenuation of the stimulus tone was noted. The broken line above 4.0 kHz is an extrapolation based on indirect observations of the attenuation. Such indirect assessment was based on the presence of oscillations in the reflex response. For lower fre

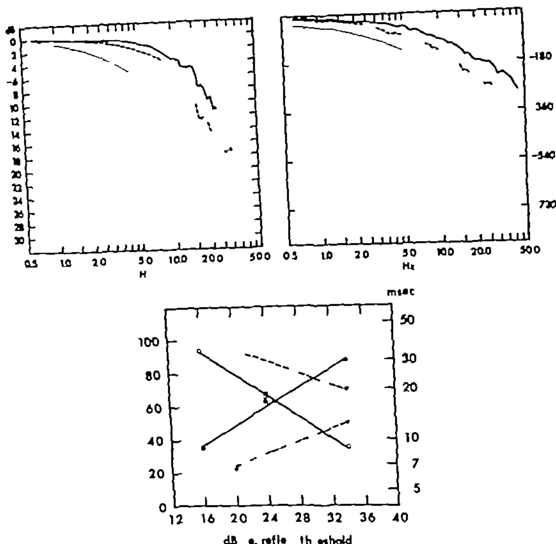


Fig. 3. *Upper graphs.* Frequency transfer function for onset of open-loop step response to contralateral stimulation with 2.0 kHz stimuli (Bode plot). Amplitude of sinusoidal components as function of frequency is shown to the left and phase shift to the right. ——— *112 dB SPL, 99 % of maximal impedance change response amplitude,* - - - 102 dB SPL, 89 % ..... 94 dB SPL, 50 %. *Lower graph.* Parameters of mathematical model for open-loop properties of the total reflex (circles, continuous lines) and the isolated TT reflex of the same animal (triangles, broken lines). Filled symbols show a (=b), left scale. Open symbols show latency T, right scale.

tinued step responses to onset of a tone burst at three different intensities: 112 dB SPL (giving impedance change of 99 % of maximal response: continuous line), 102 dB SPL (89 %: broken line), 94 dB SPL (50 %: dotted line).

The amplitude transfer functions were characterized by cut-off frequencies which in this case increased from 2.5 Hz to 9.4 Hz as the stimulus intensity was increased from 16 to 34 dB above reflex threshold. The slope of the high frequency roll-off was about — 12 dB/octave.

The phase transfer functions were characterized by the frequency where the phase shift reached —180°. This frequency varied with stimulus intensity much the same way as the

tively by observation of reflex responses and b) quantitatively by calculating frequency transfer functions and mathematical models. Due to the *nonlinearities observed qualitatively* the quantitative analysis had to be accomplished at several amplitude levels and separately for onset and decay The open loop system was subjected to the most thorough analysis which however could only be performed for the crossed reflex system. The difference between ipsilateral and contralateral reflex properties was determined for the closed loop system and thereafter used to determine the ipsilateral open loop reflex properties. Furthermore, separate analyses of the total reflex, the isolated St reflex and the isolated TT reflex, were made. The emphasis was placed on the total reflex

1 Qualitative studies (I II)

Observations of the reflex responses gave basic information about their time course. The responses obtained with the St intact in the stimulus ear (closed loop) often showed oscillations in the responses in both ears. They were most prominent at 0.5 kHz but were seen up to 8 0 kHz. Their frequency increased, as a function of sound level, *an effect which was most prominent* at stimulation with low sound frequency Their amplitude increased somewhat when the TT was cut in the stimulus ear The isolated TT rarely showed oscillations.

The open loop responses were obtained in the contralateral ear after inactivation of the muscles in the stimulated ear Denervation of the St in the stimulus ear abolished the oscillations in both ears.

The time course of the responses showed that nonlinear elements existed in the reflex loop Two types of nonlinearities were observed (a) the rise time decreased at increased sound intensity and (b) the onset of the responses was usually faster than the decay

No differences were found in the open-loop properties between the St reflex and the total reflex. The isolated TT differed from the total reflex in being slower and less dependent on level and direction of stimulus change

2 Quantitative studies (III)

Certain basic properties were observed directly in the time course of the responses. The value of essential parameters as well as a mathematical model of the dynamic properties of the middle ear muscle reflex activity were determined from the frequency transfer functions. Due to the nonlinearities, generally valid models of the reflex could not be designed The characteristics of the system in response to stimuli with rapidly varying amplitude were concluded to be modelled more adequately than those in response to slowly varying stimuli. Experimental evidence was available to allow the assumption that the reflex system behaved approximately linearly for the former signals. The onset and the decay of step properties were determined separately in response to the onset or the decay of stimulus tone bursts. Only a small number of animals were analysed quantitatively They were, however selected on the basis of their time functions and regarded to represent typical, or in some cases illustrative, examples of reflex properties.

a The onset open-loop frequency transfer functions were calculated from the crossed reflex responses *after inactivation of the muscles* in the stimulated ear It appeared that it was *sufficient to denervate* the St alone to obtain the open loop characteristics. Since only the crossed reflex system transfer properties could be obtained directly the ipsilateral open loop characteristics were *computed by correcting* those of the contralateral reflex for the differences between ipsilateral and contralateral reflex systems. This correction was obtained from the closed loop system (see next section) Since the analysis was made in the frequency-domain, the correction could be *accomplished simply by* subtraction of amplitudes (in dB) and phase angles

Figure 3 shows the frequency-domain transfer function of the crossed total middle ear reflex open loop system of one animal Amplitude *characteristics are shown in* the left upper graph and phase angles in the right upper graph The transfer functions were obtained from differen

frequency-specificity of the dynamic properties of the reflex arc.

b. The decay frequency transfer functions were described by the same general type of transfer function as the onset properties. The decay properties were slower than the onset properties and, in contrast to onset, the time constants became longer at increases in the sound level. The latency of the decay however was shorter than that of the onset. This difference might indicate that it took some time to reach threshold for the neurons of the reflex arc and also to take up slip in the mechanical response during the contraction. Thus, the relaxation latency was probably a better expression of the pure transport time than onset latency. It was less dependent on stimulus intensity than the onset latency and its value ranged from 5 to 10 msec.

For the isolated TT reflex, the onset and decay properties differed less from each other than was the case for the total reflex. The onset and the decay responses of the isolated TT reflex could be described by the same models, the only difference being the parameter values.

c. The closed-loop frequency transfer functions were obtained for the ipsilateral and the contralateral total reflex, the TT reflex and the ipsilateral St reflex. The amplitudes of the computed transfer functions of the total reflex and the isolated St reflex in the closed-loop situation showed an intensity dependent resonance peak. At 2.0 kHz this peak could only be seen in responses which were above 80 % of maximal impedance change. At 0.5 kHz clearcut peaks were seen at response amplitudes above about 30—40 % of maximal response. The frequency of the peak increased up to about 20 Hz as the stimulus level was increased. The lower frequency limit was 15 Hz at 2.0 kHz and about 8 Hz with a 0.5 kHz stimulus tone. There was good agreement between the oscillation frequency of the closed loop system and the frequency for which the phase shift of the open system was —180°. On two occasions, the isolated TT reflex transfer function showed a resonance peak. The frequency was about 10 Hz.

The closed-loop characteristics were studied ipsilaterally as well as contralaterally. Quantitative comparisons could thus be made and formed the basis for the above-mentioned calculation of the ipsilateral open-loop characteristics from the crossed reflex data.

C. DIFFERENCES BETWEEN UNCROSSED AND CROSSED REFLEX (I, III)

It was shown that the ipsilateral reflex had a somewhat higher sensitivity to sound than the crossed reflex. This difference was observed both in the total reflex and in the bilaterally isolated TT reflex and it increased towards low frequency and high intensity. The differences in the threshold of the total reflex were small (less than 2 dB), but significant at 0.5 and 2.0 kHz ($p < 0.0001$). At 80 % of maximal amplitude, it was about 5 dB (at 0.5 kHz) which corresponded to a difference in response amplitude of nearly 20 %, *i.e.* when the ipsilateral response is 80 %, the crossed response is 60 % of maximal ipsilateral amplitude. The maximal response amplitude obtained in the contralateral ear was only at the most a few per cent below that of the ipsilateral reflex. It could not be excluded that they would reach the same amplitude at higher sound levels than those available.

The dynamic properties of simultaneously recorded ipsilateral and contralateral reflexes were also found to differ. The amplitude transfer function of the crossed total reflex and of the crossed isolated TT reflex were slightly attenuated compared to the corresponding ipsilateral reflex obtained at the same sound intensity.

For the total reflex this difference was more pronounced at high sound intensities, whereas it was nearly independent of intensity for the TT reflex. The phase shift was also greater for the crossed reflex. The differencies both in amplitude and phase response are compatible with an additional neuronal link in the crossed St reflex arc (Borg, 1972 e).

cut-off frequency It increased from 7 2 to 20 6 Hz in the intensity range studied Thus, the results showed that the system became faster the higher the stimulus intensity the cut-off frequency increased and the phase shift decreased at a particular frequency

On the basis of the frequency transfer function a mathematical model was designed to describe the middle ear reflex system It was found that the response of the reflex could be approximated by a second-order system with a transport delay

$$G_0(j\omega) = \frac{Ke^{-T_1 j\omega}}{(j\omega + a)(j\omega + b)}$$

The parameters T_1 a and b were found to be dependent on stimulus intensity K was not determined in these calculations K/ab was in other experiments estimated to about 4 (11)

The lower graph of Fig. 3 shows the values of the parameters of the model as a function of *stimulus sound intensity The filled symbols* show inverted values of time constants (left scale) and the open symbols show the latency (right scale, logarithmic) The abscissa shows sound level in dB re. the threshold of the total reflex The continuous lines show the onset properties of the total reflex the broken lines show onset properties of the isolated TT reflex of the same animal The parameters were approximated by straight lines by the least mean-square criterion

It is seen that parameters a b increased (the time constants, the inverted values of a and b decreased) as sound level increased This means that the responses became faster The latency (T_1) decreased simultaneously

The isolated TT reflex properties could also be described by a second-order differential equation with a transport delay The parameters were smaller (broken lines of Fig. 3 lower graph) *i e* the contraction was slower and the latency was longer than for the total reflex. The parameters were dependent on intensity

$\text{Log } T_1 = -0.019\,x - 1.20$

$a\ (= b) = 1.81\,x + 0.60$

x is intensity in dB re TT threshold The variation in the values of the parameters as a function of sound level was less for the model of the isolated TT than for that representing the total reflex. In the case shown in Fig. 3 the isolated TT reflex threshold was 7 dB higher than the threshold of the total reflex A compensation for this difference in excitability (shift of the broken lines 7 dB to the left) decreased the difference in parameters between the total reflex and the isolated TT reflex but did not totally abolish it

Figure 3 shows the open loop properties of the crossed reflex. The ipsilateral reflex transfer function was obtained for the total reflex after subtracting the transfer properties of the crossing neural connections. By this procedure the values of the intensity dependent parameters for the model of the ipsilateral total reflex were obtained (another animal)

$$\text{Log } T_1 = 0.026\,x - 1.20$$

$$a\ (= b) = 6.54\,x - 24.9$$

x is in dB re. reflex threshold. One example of transfer function of ipsilateral total reflex is shown in Fig. 1 (lower graphs) The dots show experimental values after correction for difference between ipsilateral and contralateral systems, and the continuous lines show the approximated model.

The dynamic properties of the St reflex were assumed to be closely similar to those of the total reflex. Thus, these two situations could be represented by the same model This statement was based on comparisons of the closed loop transfer functions and time-course of open loop responses.

The results of experiments with stimuli at different frequencies implied that the onset step response properties were dependent on the frequency of the stimulus tone The open loop properties obtained with 0.5 kHz stimulus were slower and had lower cut-off frequencies. The frequencies where a —180 phase shift was reached were lower than those obtained at 2.0 kHz. The number of available experiments analysed quantitatively was too small to allow definite conclusions to be drawn on this point. These results, however tentatively indicate a

frequency-specificity of the dynamic properties of the reflex arc.

b. The decay frequency transfer functions were described by the same general type of transfer function as the onset properties. The decay properties were slower than the onset properties and, in contrast to onset, the time constants became longer at increases in the sound level. The latency of the decay however was shorter than that of the onset. This difference might indicate that it took some time to reach threshold for the neurons of the reflex arc and also to take up slip in the mechanical response during the contraction. Thus, the relaxation latency was probably a better expression of the pure transport time than onset latency. It was less dependent on stimulus intensity than the onset latency and its value ranged from 5 to 10 msec.

For the isolated TT reflex, the onset and decay properties differed less from each other than was the case for the total reflex. The onset and the decay responses of the isolated TT reflex could be described by the same models, the only difference being the parameter values.

c. The closed-loop frequency transfer functions were obtained for the ipsilateral and the contralateral total reflex, the TT reflex and the ipsilateral St reflex. The amplitudes of the computed transfer functions of the total reflex and the isolated St reflex in the closed loop situation showed an intensity dependent resonance peak. At 2.0 kHz this peak could only be seen in responses which were above 80 % of maximal impedance change. At 0.5 kHz clearcut peaks were seen at response amplitudes above about 30–40 % of maximal response. The frequency of the peak increased up to about 20 Hz as the stimulus level was increased. The lower frequency limit was 15 Hz at 2.0 kHz and about 8 Hz with a 0.5 kHz stimulus tone. There was good agreement between the oscillation frequency of the closed-loop system and the frequency for which the phase shift of the open system was —180°. On two occasions, the isolated TT reflex transfer function showed a resonance peak. The frequency was about 10 Hz.

The closed-loop characteristics were studied ipsilaterally as well as contralaterally. Quantitative comparisons could thus be made and formed the basis for the above-mentioned calculation of the ipsilateral open-loop characteristics from the crossed reflex data.

C. DIFFERENCES BETWEEN UNCROSSED AND CROSSED REFLEX (I, III)

It was shown that the ipsilateral reflex had a somewhat higher sensitivity to sound than the crossed reflex. This difference was observed both in the total reflex and in the bilaterally isolated TT reflex and it increased towards low frequency and high intensity. The differences in the threshold of the total reflex were small (less than 2 dB) but significant at 0.5 and 2.0 kHz ($p < 0.0001$). At 80 % of maximal amplitude, it was about 5 dB (at 0.5 kHz) which corresponded to a difference in response amplitude of nearly 20 %, *i.e.* when the ipsilateral response is 80 %, the crossed response is 60 % of maximal ipsilateral amplitude. The maximal response amplitude obtained in the contralateral ear was only at the most a few per cent below that of the ipsilateral reflex. It could not be excluded that they would reach the same amplitude at higher sound levels than those available.

The dynamic properties of simultaneously recorded ipsilateral and contralateral reflexes were also found to differ. The amplitude transfer function of the crossed total reflex and of the crossed isolated TT reflex were slightly attenuated compared to the corresponding ipsilateral reflex obtained at the same sound intensity.

For the total reflex this difference was more pronounced at high sound intensities, whereas it was nearly independent of intensity for the TT reflex. The phase shift was also greater for the crossed reflex. The differencies both in amplitude and phase response are compatible with an additional neuronal link in the crossed St reflex arc (Borg, 1972 e).

General discussion

The results of the present study will be discussed in four parts. a) they will be related to other information on the physiology on the middle ear reflexes of animals and man, b) present knowledge will be compiled as a phenomenological description of the rôle of the acoustic middle ear reflexes in the auditory system c) the acoustic middle ear reflexes will be related to the OC efferent system and d) some general ideas on the rôle of feed-back control in sensory systems will be presented on the basis of the present results.

A BASIC ACOUSTIC MIDDLE EAR REFLEX PROPERTIES IN ANIMALS AND IN MAN (I II III)

The information presented in the present studies on the properties of the acoustic middle ear reflexes in rabbits was obtained under conditions which justify comparisons to available results in man. The recording and stimulating technique used was identical to that used earlier in several studies in man (Møller 1961 1962 a 1962 b Borg, 1968)

1 Excitability (I)

Excitability of the St reflex (measured as the total reflex) of the rabbit was found to be significantly higher *i.e* the threshold was lower than that of man by the order of 10—20 dB over a wide frequency range In man, an acoustic TT reflex is not regularly present. According to Lidén et al (1970) it can be recorded in a small fraction of normal subjects (13 %) Other authors deny the presence of a specific acoustic TT reflex in man. They have only found TT responses as part of startle reactions to acoustic and nonacoustic stimuli (Klockhoff 1961 Djupesland 1967) Thus, the interspecies differences are at least equally prominent with regard to the acoustic TT reflex as for the St reflex.

These comparisons are valid for ipsilateral pure tone stimulation. Noise stimuli (Møller 1962 a McRobert et al., 1968 Flottorp et al. 1971) and bilateral stimulation (Møller 1962 a) have been used in man and are likely when used in conjunction to lower the threshold by up to 20 dB There is no experimental data in support of an assumption that the relation of the excitability between rabbit and man would be different for complex stimuli than for pure tones.

Studies in the cat show extremely variable results which probably are due both to the methods used (restrainment of animals, free field stimulation, chronically implanted electrodes) and to a greater variability inherent in the reflexes of cats. It was concluded that the average excitability does not significantly differ between the cat and the rabbit. There is thus a generally higher excitability of the middle ear muscles in animals than in man. Consequently great care should be taken in the application of data obtained from animals with regard to the function of the reflexes in man in order to avoid overestimation of situations wherein the muscles are active.

2 Regulation of sound transmission (II).

The attenuation of sound transmission is similar in the rabbit and man with respect to efficiency of regulation, which is about 0 7 dB/dB under closed loop conditions in both species (man Borg, 1968 rabbit II) This equality refers to low frequency sound

In the rabbit the attenuation of sound transmission was found to extend at least up to 8 0 kHz (II) Lorente de Nó (1935) observed reflex responses with oscillations in the rabbit as far as to 16 kHz, which is an indirect proof for attenuation at this frequency (II) The oscillations at this frequency in the example shown were, however minute. Evidence from other

studies both in the anesthetized cat (Gisselsson et al 1957) and the rabbit (Price, 1966) support the conclusion of attenuation of high frequencies in animals.

In studies on human postmortem temporal bones, Neergaard et al. (1963) found influence of forces applied to the St on sound transmission up to 3.5 kHz. In a later study Cancura (1970) did not in general find an influence on sound at and above 2.0 kHz. This failure is in accordance with results of studies using non-acoustic activation of the muscles in the middle ear in human (Pichler & Bornschein, 1957 Reger 1960) It is, however possible that acoustic activation of St in normal humans gives more effective contractions than can be obtained by nonacoustic stimuli and in postmortem temporal bones In such a case, like in the rabbit, a very high level of St activity might influence also frequencies well above 2.0 kHz.

Eventhough there seem to be differences between man and animals both with regard to threshold for activation of the muscles and frequency range of their influence on sound transmission it should be noted that the threshold for influence on sound transmission is about the same (90—100 dB SPL for pure tones) This high threshold value does, of course, not imply that only high intensity sounds are influenced by the muscles On the contrary weak components are attenuated if they coincide with or appear shortly after a strong sound

3 Dynamic properties (III).

The dynamic properties differ markedly between rabbit and man Since no definite data on the onset open-loop transfer function is available in man (the best approximation available is presented by Møller 1962 a) and cat, the closed loop resonance frequency is appropriate to use for comparison In the rabbit it was about 18—22 Hz and in man about 5 Hz (Møller 1962 a). Oscillations appear more regularly in the St than in the TT (Wersäll, 1958 I) In the cat, they have been observed at a frequency of about 15—20 Hz (Okamoto et al., 1954 Eliasson & Gisselsson, 1955) and they seem to be more pronounced in the TT than the St in this animal.

Not only do the onset dynamic properties of the reflex in man and rabbit differ but the stability of responses during prolonged (10 seconds to 1 minute) constant stimulation is also in variance. Above 1.0 kHz the reflex responses in man (Anderson et al., 1969 Tietze, 1969) and in the cat (Simmons, 1963) have been found to fail to keep a constant amplitude in contrast to the conditions in the rabbit (Borg & Møller 1968). Only excessive stimulation (130—140 dB SPL) can produce a similar decay in the reflex responses in the rabbit (Wersäll, 1958)

Dynamic nonlinearities were prominent, specially in the total reflex and the isolated St reflex. They were of two types, dependent on amplitude and direction of change of amplitude. On the basis of earlier experiments (Borg, 1971 b) it was concluded that linear methods could be used to analyse the reflex properties for rapidly rising stimuli Such an approach to analysis of a nonlinear system has not been used earlier to the authors knowledge. It leads to a mathematical model of the reflexes valuable for rapidly rising and falling stimuli throughout the dynamic range of the reflexes. This has not been accomplished earlier for nonlinear reflex systems.

B FUNCTIONAL ROLE OF THE MIDDLE EAR REFLEXES

The basic physiology of the middle ear reflexes has been fairly extensively studied. On the other hand, considerably less attention has been paid to analysing their rôle for perception of sound. Several theories and ideas have been advanced to describe the functional rôle of the middle ear muscles, especially with regard to the acoustic reflexes. Wever & Lawrence (1954), Jepsen (1955 1963), Kobrak (1959), Kirikae (1960), Cancura (1970) and Møller (1972) have presented comprehensive reviews of most of these theories.

The ideas cover a wide range of possibilities from listening muscles (Ostmann, 1899) and

protective devices for the cochlea (Müller 1838) to regulation of labyrinthine fluid pressure (Politzer 1861) and protection of the vestibular system from low frequency acoustic vibrations (Cancura 1970) The function of the middle ear muscles is probably relevant to some of these factors whereas others are merely of historical interest. The relevance of these theories will not be directly discussed here.

On the basis of the present results, the following functions of the acoustic middle ear reflexes have been suggested a) extension of dynamic range of the auditory system for intensity (II) b) decrease of masking of low frequency sound on high frequency sound (II) and c) influence on adaptation (II III) Most of these ideas have been presented in one form or another by earlier workers in this field

1 *Extension of dynamic range*

In this context dynamic range means the range of sound pressure level in the ear canal over which the auditory system operates adequately *e g* discriminates significant sound is not fatigued or damaged

It is shown clearly by the present experiments (II) that high intensity sound over a wide frequency range is attenuated by the middle ear muscle contraction The efficiency of this attenuation is such that a 10 dB increase of sound level above threshold for attenuation results in only a 3 dB increase of actual sound input to the cochlea. It can be immediately realized that this feed back attenuation tends to increase the dynamic range of the afferent auditory system

The rôle of the extention of dynamic range has chiefly been described in terms of protection from fatigue or structural damage to the cochlea (for reviews, see Wever & Lawrence, 1954 Cancura, 1970) The attenuation provided by the middle ear muscles i[illegible] no doubt of protective value decreasing da[illegible]ge and fatigue to the cochlea It has been w[illegible] established in animal experiments (Kato 1913 Taruya, 1953 Hilding, 1961) as well as in human experiments (Fletcher & Riopelle, 1960 and others) that the ear suffers less damage and fatigue from sound exposure if the muscles are contracting during the sound However this effect has been regarded as unimportant by several authors with reference to the rare occurrence of strong sound in nature, the long latency of the reflex and its fatiguability (see *e g* Cancura, 1970) Especially it has been pointed out that the ear is most sensitive to damage at high frequency (around 4 kHz) in man, thus outside the frequency range usually considered to be influenced by middle ear muscle contractions in man. It has, however been overlooked that there might be a casual relation between the great resistance of the cochlea to fatigue at low frequency and the attenuation provided by the middle ear muscles in this frequency range. In fact, a significant increase in susceptibility to low frequency sound exposure has been observed in subjects with decreased or abolished St contractions in man (Lehnhardt, 1959 1960 Smith et al., 1966 Mills & Lilly 1971 Zakrisson & Borg, in manuscript) It is also interesting to observe that the maximal post-exposure shift of hearing threshold occurred within the range of frequencies most essential for understading of speech when the St was paralyzed, but mainly above these frequencies when its function was normal (Lehnhardt, 1960)

A great sensitivity to low frequency sound exposure in the deeply anesthetized cat (depressed middle ear reflexes) has also been found (Price, 1972) In addition, evidence for the existence of a threshold phenomenon in deterioration of cochlear function was obtained in those experiments. Exposing sound above this level (in the range of 140 dB SPL at 0.5 kHz) gave a very prominant decline in the cochlear microphonic potentials of post-exposure test sound. No information was, however presented on a relationship between middle ear reflex attenuation of sound transmission and the threshold for extensive cochlear fatigue.

It is probable that protection is most adequate in relation to sound produced by the individual itself. This idea has gained considerable support by the work of Henson (1965) in the bat (see further p 25)

Protection is, however only one aspect of the extension of the dynamic range of the auditory system. Others, such as improvement of discrimination should also be regarded.

The implication of the extension of dynamic range for the resolution of complex sound are poorly understood since few studies have analysed the auditory discrimination function at high intensity and still fewer have done this with the aim to study the middle ear reflexes

Nonlinearities and distortion products are probably important in determination of the upper limit of the dynamic range of the auditory system. The middle ear is probably not critical in this respect since it has been found to be linear up to at least 130 dB SPL in deeply anesthetized cats in a wide frequency range (Guinan & Peake, 1967) The cochlea, however has long been known to be nonlinear at much lower intensities (see *e g* a recent study by Rhode, 1971)

Worthington and Dallos (1971) used cochlear microphonics to study the sources of nonlinearity in the inner ear of the guinea pig. One type of nonlinearity appeared at about 80—90 dB SPL. The close correspondence to the threshold for the middle ear reflex is to be noted In an earlier study it was shown that contractions of TT decreased the amplitude of harmonics in the cochlear microphonics of the guinea pig (Stevens & Newman, 1936)

A more direct hint to the rôle of the middle ear reflexes for discrimination at high intensities is obtained from a recent study in man It was shown that subjects with unilateral St paralysis (in Bell's palsy) suffer a significant decrease in their ability to discriminate nonsense monosyllables above about 100 dB SPL (time constant of 100 msec) in the ear with St paralysis as compared to the other ear with normal St function (Borg & Zakrisson, in manuscript) Below about 100 dB SPL discrimination was equal on both sides The discrimination scores were found to be normalized after the function of the St had been regained These results might indicate that the middle ear reflexes prevent a great increase in the generation of distortion products at high sound levels. A close correspondance was found between the threshold for activation of St in the normal ear in response to the test words and the threshold for loss of discrimination in the ear with St paralysis. This correlation implies an adaptation of the St function to the afferent auditory system to an unexpected degree.

There has been much debate about the significance of the fact that the middle ear reflexes are only activated by fairly high level sound High threshold values have been regarded as an experimental artefact (Simmons, 1964 c) High thresholds, however appear reasonable when the high regulation efficiency is regarded. Since in man (Borg, 1968) and in the rabbit (II) only about 3 dB out of a 10 dB increase in sound level reaches the cochlea the slope of the stimulus-response curve thus decreases considerably Such a decrease in slope would decrease sensitivity for small differences in intensity Evidently from the viewpoint of intensity discrimination the reflex thresholds are expected to be above the range of commonly significant sounds The detailed consequences of having a low reflex threshold are difficult to predict since the time characteristics of the reflexes as well as those of the ear must be considered. It can be studied in experiments on subjects with St paralysis where the middle ear reflexes are substituted by an electronic analogue in which the control of sound transmission has variable threshold. Such work is in progress.

The threshold of the reflex attenuation of sound transmission must be regarded also in relation to the natural acoustic environment of animals and man. As a rule the highest sound levels they obtain are coincident with vocalization. In man high levels are encountered in everyday life *e.g.* with children, in excited discussions and laughter In such conditions the attenuation provided by the middle ear muscles can be of importance both for an improvement of discrimination and prevention from fatigue. It can be suggested as a topic for further research to compare intensity range of significant sounds and the reflex thresholds in vari-

protective devices for the cochlea (Müller 1838) to regulation of labyrinthine fluid pressure (Politzer 1861) and protection of the vestibular system from low frequency acoustic vibrations (Cancura, 1970) The function of the middle ear muscles is probably relevant to some of these factors whereas others are merely of historical interest. The relevance of these theories will not be directly discussed here.

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unilateral St paralysis (associated with Bell's palsy) and normal hearing thresholds show a decrease in discrimination scores on the paralysed side compared to their normal ear. The threshold for the difference was at speech level of 90—100 dB SPL and noise level of 80—90 dB SPL (Borg & Zakrisson, in preparation)

The middle ear reflex function can thus be considered as compensation for a "weakness" of the cochlear function, the mechanisms for frequency analysis introduce a masking effect that at high intensity becomes very extensive. As a speculation, it can be suggested that feed back regulation provides the most economic compensation method with sufficient efficiency

3. *Adaptation.*

In this context adaptation means a decrease of response of the auditory system following sound stimulation. Due to the latency and the rise time of the middle ear muscle reflex response, the attenuation of sound does not occur immediately after the onset of the sound, but only after several tenths (rabbit, III) or hundreds (man, Møller 1962 a) of milliseconds. Thus, mainly those components are attenuated which follow a strong, reflex-eliciting sound. This effect thus contributes adaptation to the auditory periphery (see also Holstein et al 1969) The contrast in the temporal pattern of sound is increased if a strong sound precedes a weaker one. Rapid changes in intensity of a sound are enhanced at the expense of sound with constant or slowly varying intensity

It is sometimes reported by patients with unilateral total St paralysis that they perceive an accentuation of echoes (Borg, unpublished). A suppression of an echo can be regarded as an example of adaptation. The perception is localized to the head of the patient and is elicited by external sound as well as by the patient's own voice. The echoes of external sound disappear if the external meatus is occluded, but the voice echoes remain and are increased. However no measurements are available to illustrate this point objectively and quantitatively

According to Wigand and Borucki (1965), separation of double clicks is deteriorated in subjects who have been stapedectomized or who have a Bell's palsy. This effect was ascribed to an increase in duration of the response to the clicks when the middle ear muscles were paralyzed. The evidence presented in animal experiments (Wigand, 1965 Wigand & Borucki, 1965) for such an increase in duration does not appear convincing since the recordings shown unfortunately have insufficient signal-to-noise ratio to allow for these conclusions and to differentiate an increased damping from merely the well-known reduction in amplitude (II). Furthermore, such a function of the middle ear muscles in man presupposes a *considerable* degree of spontaneous tonic middle ear muscle contraction in man. Electromyographic recordings show however very slight or no activity in the absence of sound at rest (Fisch & Schulthess, 1963 Salomon & Starr 1963)

4. *The relation between m. stapedius and m. tensor tympani reflexes*

The present results are in agreement with most earlier studies in showing that the St is more excitable by sound than the TT (I). It has also a dominating rôle in the regulation of sound transmission through the middle ear (II). It can be observed that the St in man (Borg, 1968) has equally great influence on transmission of low frequency sound (0.7 dB/dB at 0.5 kHz) as has the St and TT together in rabbit (approximately 0.5 and 0.2 dB/dB, respectively at 0.5 kHz). It might thus be fruitful to consider the lack of acoustic TT reflex activity in man in this relation: the St alone provides sufficient regulation which can be interpreted so there is no need for an acoustic TT reflex.

Some occasional observations of the present study (I) in conjunction with recent tympanometric studies by Ingelstedt & Jonson (1967) might suggest a mainly ventilatory function of the TT

ous species of animals. It is the authors impression that small mammals (cats and rabbits) in general are surrounded by weaker sounds than man. If this assumption and the preceding argumentation are valid it is compatible with the lower reflex threshold observed in cats and rabbits than in man (I)

Thus the acoustic middle ear reflexes can play a rôle to relieve the consequences of imperfections in the afferent auditory system, the middle ear and chiefly the cochlea at the upper end of the dynamic range. These imperfections can be assumed to be more severe, without deteriorating the performance of the system as a whole, in a receptor with feed back regulation than in a corresponding receptor without such a compensatory mechanism The discrimination ability is directly increased by the reflexes for high level sound and performance below reflex threshold might be indirectly improved (see also p 29)

2. *Decrease of masking*

It has long been known from psychoacoustic studies that low frequency sound masks high frequencies to a much higher degree than the reverse (for review of the earlier literature, see Stevens & Davis, 1938 and for a modern review see Scharf 1971) It is generally regarded to be due to the vibration pattern of the basilar membrane. The masking increases rapidly above 40 to 60 dB sensation level (Ehmer 1959) A reduction in the low frequency components of complex sound would therefore increase the detectability for the various spectral components of the sound over a wide frequency range. The validity of this assumption is supported by the abnormally good hearing in noise observed in patients with low frequency hearing loss due to middle ear pathology (paracusis Willisii de Maré & Rösler 1950)

In this relation the fact makes sense that high frequency sound is most effective in eliciting the muscle contraction (rabbit I) although the contraction most readily attenuates low frequency sound (II) In man (Møller 1962 b) the difference between the thresholds for low and high frequency is similar to that in the rabbit (I) Furthermore, also in man low frequency sound is attenuated by all degree of muscle activity (Borg, 1968) whereas high frequencies are, if at all, only attenuated at intensities far above reflex threshold (Borg, 1968) This interaction between low and high frequency can be described as equivalent to lateral inhibition (II) Of course, the feed back attenuation — low frequency sound is attenuated by reflex activity elicited by the low frequency sound itself — is also important in this respect. Stevens & Davis (1938) suggested a reduction of masking to be a possible advantage for hearing provided by the middle ear muscles.

The magnitude of the antimasking effect of the reflexes can be estimated on the basis of the results gained in the present study (and the results by Borg, 1968) and from masking experiments, e.g. those by Ehmer (1959) and others. A 20 dB reduction in intensity of the masking sound (from 80 to 60 dB sensation level) gives a reduction in masking that is equivalent to a 70 % reduction of the area of masking in the logarithmic frequency intensity plane.

The activation of the middle ear muscles by lightly touching the skin around the ear (Kato 1913 Lüscher 1929 Klockhoff 1961 Djupesland 1967) might also be relevant in this connection. Objects or air streams touching the head are likely to produce some masking noise which thus is attenuated by the middle ear muscle contractions.

The rôle of St reflex for discrimination of speech in low frequency noise was investigated by Lidén et al. (1964) in two groups of patients that had been stapedectomized with two different methods. In one of the methods the St tendon was preserved in the other it was cut. They found that discrimination scores in noise in the patient with St tendons preserved was more seldom deteriorated by the operation than in those with the tendon cut. The authors concluded that their results showed an antimasking effect of the St in man. Preliminary results from discrimination measurements of nonsens words in 700 Hz lowpass filtered noise in subjects with

and keeps the receptor region in suitable length to retain its sensitivity even during shortening of extrafusal muscle fibers (for a recent review see Granit, 1970). One aspect of the rôle of these mentioned efferent control systems is thus that they improve the resolution without loss of dynamic range and to a low cost for the organism.

The two efferent systems influencing the response of the cochlea, the middle ear muscles and the OC efferents, can be viewed in relation to range and resolution of the intensity of sound. The OC efferents increase the slope of the stimulus-response curve of the cochlea by depressing response chiefly to low-intensity sound (see e.g. Wiederhold, 1970. Borg, 1971 a). Sensitivity to changes in intensity can thereby be assumed to be enhanced at expence of a temporary increase in threshold.

The middle ear reflexes decrease the slope of the stimulus-response curve above a threshold value of 90—100 dB SPL (II. Borg, 1968). This "compression" allows the cochlea to operate with a steeper stimulus-response curve in the intensity range *below* the reflex threshold than if the slope was constant in the whole dynamic range of the cochlea. The resolution of sound intensity will thereby indirectly be improved in the range below the reflex threshold, the range of most significant sounds. It will also be kept at an acceptable level in the high intensity range where the cochlea operates poorly when deprived of middle ear muscle feed-back regulation (see page 25). Thus, the control systems in the auditory periphery can be conceived also as improving the resolution without decrease of dynamic range.

The results obtained in the present study emphasize as an important function of sensory system control mechanisms the improvement *of resolution at a low cost for the organism* and without decrease of dynamic range.

Summary

1. *The* acoustic middle ear reflexes were analysed in nonanesthetized unrestrained rabbits with respect to their excitability, influence on sound transmission and dynamic properties. Ipsilateral and contralateral contractions of the two middle ear muscles, m. stapedius and m. tensor tympani in separation and in conjunction (the total reflex), were recorded *simultaneously* by measuring changes in the acoustic impedance of the ear. Bursts of pure tone in the frequency range 0.5 to 12.0 kHz at intensities up *to 125* dB SPL were used as stimuli.

2. The mean value of the threshold (defined as *10%* of maximal response) of the total reflex was found to be 98. dB SPL at 0.5 kHz and decreased with increasing *frequency at a* rate of about 1. db/octave *to 2.0 kHz*. Above 4.0 kHz it was nearly constant at about 70 dB SPL.

3. The excitability of the isolated m. stapedius reflex did *not differ* from that of the total reflex whereas *the m. tensor tympani had* a 10 dB *higher threshold in* the whole frequency range.

4. Contractions *of the* middle ear muscles *attenuated the sound transmission* through the middle ear above 90—100 dB SPL irrespective of sound frequency up *to* at least 8.0 kHz. The middle ear muscle reflex, working as a closed-loop control system, provided about a 0.7 dB attenuation per 1.0 dB increase in sound level above the threshold for the attenuation throughout *a* wide *frequency range*. The equivalent efficiency of regulation of the open-loop system was about 2 dB/dB.

5. The dynamic properties of the reflexes were nonlinear but they could be modelled by second-order differential equations having

C. THE ACOUSTIC MIDDLE EAR REFLEX IN RELATION TO OTHER AUDITORY SYSTEM CONTROL MECHANISMS

The efferent regulators of the auditory system analysed experimentally to some extent — the OC efferents and the middle ear muscles — have both common and different properties. Both are activated as reflexes by auditory stimuli and both are influenced by the CNS (Fex, 1962, 1965 Rupert et al 1968 Borg, 1971 a) Both probably decrease noise masking (regarding the OC efferents, see Dewson 1968 Trahiotis & Elliott, 1970 Nieder & Nieder 1970· Borg, 1971 a see, however Igarashi et al 1972) The two regulators have been found to differ *e g* regarding their effect on latency of auditory nerve response to clicks (N_1) (Desmedt et al., 1971) The OC efferents attenuate N_1 without prolonging the latency in contrast to St contractions. The frequency intensity region where their maximal effects occur also differs. The OC efferents have their main effect on weak sounds in high frequency range (above 2.0 to 3 0 kHz, Wiederhold 1970) whereas the middle ear muscles affect sound of all intensities chiefly of low frequencies (below about 1 0 kHz, II) Higher frequencies are attenuated only at maximal middle ear muscle contraction

On anatomical grounds the OC efferents can be proposed to exert their influence with greater frequency specificity than the high pass filtering provided by the middle ear muscles, since each efferent nerve fiber extends only over a small portion of the basilar membrane (Spoendlin, 1970) Furthermore, there is evidence that the organization of the neuronal pathways is fundamentally different for the activation of OC fibers and middle ear muscles by sound (Warr 1969 Osen & Roth 1969 Borg, 1972 d 1972 e)

As yet general statements are premature on the functional relationship between the middle ear reflexes and the OC efferents. The prominent anatomic and physiologic differences imply however that they represent partly different aspects of control of afferent auditory activity

D GENERAL ASPECTS ON CONTROL IN SENSORY SYSTEMS

Two important properties of sensory systems (a) high sensitivity to small changes in stimulus (resolution) and (b) responsiveness over a wide range of parameters of the physical stimulus (dynamic range) imply contradictory functional demands on the sensory systems. A high resolution necessitates *e g* a steep stimulus response relation A large dynamic range implies low threshold and no saturation within the physiological range, which thus tends to decrease the slope of this function. This problem has been solved in various ways for different sense organs.

The human visual system has a high spatial resolution in the fovea centralis. The resolution in the peripheral visual field is considerably lower but sufficient to detect objects suitable for further analysis. By means of efferent mechanisms, the extra-ocular muscles, the region of high resolution is moved to analyse the object.

Theoretically similar effects could be achieved in other ways. For instance, the retina could have the same extremely high density of cones peripherally as centrally and a corresponding amount of optic nerve fibers. Unaltered refinement of central analysis performed simultaneously throughout the visual field offers an equally good or a better solution to the compromise between range and resolution than does the eye position control system However it subjects the central nervous system to a good deal of extra work.

The gamma-efferents of the muscle spindles constitute another system which from a restricted *point of view* can be regarded to have a function to improve the compromise between the demands on range and resolution. Impulse flow in the gamma-efferent shortens the contractile portion of the intrafusal muscle fiber

and keeps the receptor region in suitable length to retain its sensitivity even during shortening of extrafusal muscle fibers (for a recent review see Granit, 1970). One aspect of the rôle of these mentioned efferent control systems is thus that they improve the resolution without loss of dynamic range and to a low cost for the organism.

The two efferent systems influencing the response of the cochlea, the middle ear muscles and the OC efferents, can be viewed in relation to range and resolution of the intensity of sound. The OC efferents increase the slope of the stimulus-response curve of the cochlea by depressing response chiefly to low-intensity sound (see e.g. Wiederhold, 1970, Borg, 1971 a). Sensitivity to changes in intensity can thereby be assumed to be enhanced at expence of a temporary increase in threshold.

The middle ear reflexes decrease the slope of the stimulus-response curve above a threshold value of 90—100 dB SPL (II. Borg, 1968). This "compression" allows the cochlea to operate with a steeper stimulus-response curve in the intensity range *below* the reflex threshold than if the slope was constant in the whole dynamic range of the cochlea. The resolution of sound intensity will thereby indirectly be improved in the range below the reflex threshold, the range of most significant sounds. It will also be kept at an acceptable level in the high intensity range where the cochlea operates poorly when deprived of middle ear muscle feed-back regulation (see page 25). Thus, the control systems in the auditory periphery can be conceived also as improving the resolution without decrease of dynamic range.

The results obtained in the present study emphasize as an important function of sensory system control mechanisms the improvement of resolution at a low cost for the organism and without decrease of dynamic range.

Summary

1. The acoustic middle ear reflexes were analysed in nonanesthetized, unrestrained rabbits with respect to their excitability, influence on sound transmission and dynamic properties. Ipsilateral and contralateral contractions of the two middle ear muscles, m. stapedius and m. tensor tympani in separation and in conjunction (the total reflex), were recorded simultaneously by measuring changes in the acoustic impedance of the ear. Bursts of pure tone in the frequency range 0.5 to 12.0 kHz at intensities up to 125 dB SPL were used as stimuli.

2. The mean value of the threshold (defined as 10 % of maximal response) of the total reflex was found to be 98 dB SPL at 0.5 kHz and decreased with increasing frequency at a rate of about 1 db/octave to 0 kHz. Above 4.0 kHz it was nearly constant at about 70 dB SPL.

3. The excitability of the isolated m. stapedius reflex did not differ from that of the total reflex whereas the m. tensor tympani had a 10 dB higher threshold in the whole frequency range.

4. Contractions of the middle ear muscles attenuated the sound transmission through the middle ear above 90—100 dB SPL irrespective of sound frequency up to at least 8.0 kHz. The middle ear muscle reflex, working as a closed-loop control system, provided about a 0.7 dB attenuation per 1.0 dB increase in sound level above the threshold for the attenuation throughout a wide frequency range. The equivalent efficiency of regulation of the open-loop system was about 2 dB/dB.

5. The dynamic properties of the reflexes were nonlinear but they could be modelled by second-order differential equations having

parameters dependent on both amplitude and direction of change of amplitude. The total reflex and the isolated m stapedius reflex had almost identical dynamic properties, whereas the isolated m. tensor tympani reflex was slower

6 The reflex properties were discussed in relation to hearing in man and other animals. The results obtained in the present study suggest three main functions of the acoustic middle ear reflexes a) extension of the dynamic range of the auditory system with respect to intensity b) decrease of masking of low frequency sound on high frequencies and c) contribution to adaptation whereby changes in intensity are enhanced In a broader sense, the results serve to illustrate that sensory system control mechanisms provide solutions of demands for high resolution and wide range at low cost to the organism

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PARTICIPANTS IN SYMPOSIUM ON MENIERE'S SYNDROME

Dr R A Bertrand Laboratoire de Labyrinthologie, Hôpital Notre-Dame, Montreal P Q Canada.

Dr R. R. A Coles Institute of Sound and Vibration Research, University of Southampton, Southampton, UK.

Dr H Denise Cliniques St. Charles, Rue Auguste Broussonnet, 34 Mont pellier France.

Professor A Drymael Vrije Universiteit van Brussel, Brussels, Belgium.

Dr H Fermin, Academisch Ziekenhuis Dijkzigt, Rotterdam 2, The Nether lands

Dr M J Flynn Clinical Research Department, N V Philips-Duphar Weesp, The Netherlands.

M I J C Frew Department of Otorhinolaryngology Newcastle General Hospital, Newcastle-upon-Tyne UK.

M D Garfield Davies Department of Otorhinolaryngology Middlesex Hospital, London W 1 UK

Dr M Gersdorff De Clinique Otorhinolaryngologique Université Catholique de Louvain, Louvain, Belgium

Dr H F J Greven Director of Research, N V Philips-Duphar Weesp, The Netherlands

Professor D Hennebert Université Libre de Bruxelles, Brussels, Belgium

Dr R. Hinchcliff The Institute of Laryngology and Otology University of London, London W C.1 UK

Dr P E Hoeksema, Algemeen Provinciaal Stads-en Academisch Ziekenhuis, Groningen, The Netherlands

Dr O R Hommes Kliniek voor Neurologie, Sint Radboud Hospital, Nijmegen, The Netherlands

M R G Hughes Department of Otorhinolaryngology Wolverhampton and Dudley Group of Hospitals, Wol erhampton, UK.

Professor L B W Jongkees Wilhelmina Gasthuis, De Universiteit van Amsterdam, Amsterdam, The Netherlands

Professor P Kluyskens Rijksuniversiteit, Ghent, Belgium

Dr K. Laemmli Oberarzt O R.L. Klinik, Kantonsspital, Zurich, Switzerland.

Dr C C Leibbrandt Kliniek voor Keel, Neus en Oorheelkunde, Academisch Ziekenhuis, Utrecht, The Netherlands.

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Dr M J Flynn Clinical Research Department, N V Philips-Duphar Weesp, The Netherlands.

M I J C Frew Department of Otorhinolaryngology Newcastle General Hospital, Newcastle-upon-Tyne, UK.

Mr D Garfield Davies Department of Otorhinolaryngology Middlesex Hospital, London W 1 UK

Dr M Gersdorff De Clinique Otorhinolaryngologique, Université Catholique de Louvain, Louvain, Belgium.

Dr H F J Geuens Director of Research, N V Philips-Duphar Weesp, The Netherlands

Professor D Hennebert Université Libre de Bruxelles, Brussels, Belgium

Dr R Hinchcliffe The Institute of Laryngology and Otology University of London, London W C 1 UK

Dr P E Hoeksema, Algemeen Provinciaal Stads-en Academisch Ziekenhuis, Groningen, The Netherlands

Dr O R Hommes Kliniek oor Neurologie, Sint Radboud Hospital, Nijmegen, The Netherlands

M R G Hughes Department of Otorhinolaryngology Wolverhampton and Dudley Group of Hospitals, Wolverhampton, UK.

Professor L. B W Jongkees, Wilhelmina Gasthuis, De Universiteit van Amsterdam, Amsterdam, The Netherlands.

Professor P Kluyskens, Rijksuniversiteit, Ghent, Belgium.

Dr K. Loennell Oberarzt O R.L. Klinik, Kantonsspital, Zurich, Switzerland

Dr C C. Leibbrandt Kliniek voor Keel, Neus en Oorheelkunde Academisch Ziekenhuis, Utrecht, The Netherlands.

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PARTICIPANTS IN SYMPOSIUM ON MENIERE'S SYNDROME

Dr R A Bertrand Laboratoire de Labyrinthologie, Hôpital Notre-Dame Montreal P Q Canada.

Dr R. R. A Coles, Institute of Sound and Vibration Research, University of Southampton, Southampton, UK.

Dr H Denise Cliniques St. Charles, Rue Auguste Broussonnet, 34 Montpellier France.

Professor A Drymael, Vrije Universiteit van Brussel, Brussels, Belgium.

Dr H Fermin Academisch Ziekenhuis Dijkzigt, Rotterdam 2, The Netherlands

Dr M J Flynn Clinical Research Department, N V Philips-Duphar Weesp The Netherlands.

M I J C Frew Department of Otorhinolaryngology Newcastle General Hospital, Newcastle-upon-Tyne UK.

M D Garfield Davies, Department of Otorhinolaryngology Middlesex Hospital, London W I UK

Dr M Gersdorff De Clinique Otorhinolaryngologique, Université Catholique de Louvain, Louvain, Belgium.

Dr H F J Geurts, Director of Research, N V Philips-Duphar Weesp, The Netherlands

Professor D Hennebert Université Libre de Bruxelles, Brussels, Belgium

Dr R Hinchcliffe The Institute of Laryngology and Otology University of London, London W C I UK

Dr P E Hoeksema, Algemeen Provinciaal Stads-en Academisch Ziekenhuis, Groningen, The Netherlands

Dr O R Hommes Kliniek voor Neurologie, Sint Radboud Hospital, Nijmegen, The Netherlands

M R G Hughes Department of Otorhinolaryngology Wolverhampton and Dudley Group of Hospitals, Wolverhampton, UK.

Professor L. B. W Jongkees, Wilhelmina Gasthuis, De Universiteit van Amsterdam, Amsterdam, The Netherlands

Professor P Kluyskens, Rijksuniversiteit, Ghent, Belgium.

Dr K. Laemmli Oberarzt O R L. Klinik, Kantonsspital, Zurich, Switzerland.

Dr C C Lebbrandt Kliniek voor Keel, Neus en Oorheelkunde Academisch Ziekenhuis, Utrecht, The Netherlands.

Dr E A Marcus Clinical Research Department, N V *Philips-Duphar* Weesp The Netherlands.

Dr E H M A Marres Kliniek voor Keel, Neus en Oorziekten, Sint Radboud Ziekenhuis, Nijmegen The Netherlands.

Dr D M Martinez Neurotology Research Laboratory Department of Otolaryngology South Western Medical School (University of Texas) Dallas, Texas, USA

Mr I McClure Department of Otorhinolaryngology Ayr County Hospital Ayr Scotland, UK

Professor H McKennis Jr Department of Pharmacology Medical School of Virginia Richmond Va, USA.

Dr J Melon De Clinique *Otorhinolaryngologique Université de Liege* Liege Belgium.

Dr G N Menon Clinical Research Department, N V Philips-Duphar Weesp The Netherlands.

Dr S C Mishra Oberarzt O R.L. Klinik Buergerspital, Basle, Switzerland

Dr A Morgon Hôpital Eduard Herriot Pavillon U Lyon France

Dr M Norre Katholieke Universiteit van Leuven Leuven, Belgium.

Professor P Pialoux Otorhinolaryngoliste des Hôpitaux à la Faculté de Médecine Paris, France.

Mrs V M Priede Institute of Sound and Vibration Research University of Southampton Southampton, UK.

Dr W M Rosinga, Director of Clinical Research, N V Philips-Duphar Weesp The Netherlands.

Mr D W Stuart Department of Otorhinolaryngology North Staffordshire Royal Infirmary Stoke-on Trent, UK.

Dr R Voegeli Spezialarzt FMH für Ohren Nasen und Halskrankheiten 4000 Basle, Switzerland.

Mr T J Wilmot Department of Otorhinolaryngology Tyrone County Hospital, Omagh Northern Ireland UK.

Dr A Ziglinas Oberarzt O R.L. Klinik, Hôpital Cantonal, *Geneva, Switzer* land.

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Dr E A Marcus Clinical Research Department, N V Philips-Duphar Weesp, The Netherlands.

Dr E H M A Marres Kliniek voor Keel, Neus en Oorziekten, Sint Radboud Ziekenhuis, Nijmegen The Netherlands.

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Mr I McClure Department of Otorhinolaryngology Ayr County Hospital Ayr Scotland UK

Professor H McKennis Jr Department of Pharmacology Medical School of Virginia, Richmond, Va, USA.

Dr J Melon De Clinique Otorhinolaryngologique, Université de Liege, Liege, Belgium

Dr G N Menon Clinical Research Department N V Philips-Duphar Weesp The Netherlands.

Dr S C Mishra Oberarzt O R.L. Klinik Buergerspital, Basle, Switzerland.

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Dr A Ziglinas Oberarzt O R.L. Klinik, Hôpital Cantonal Geneva Switzerland.

PREFACE

This supplement reports the proceedings of the Symposium on Ménière's Syndrome sponsored by N.V. Philips-Duphar and held in the Hotel Bouwes at Zandvoort in The Netherlands on Thursday 3rd September 1970. The names and addresses of the participants in the symposium are listed on preceding pages.

A connection between the sponsors of the Symposium and the drug betahistine hydrochloride is obvious insofar as much of the symposium was devoted to the pharmacology and activity of this drug. However, it was felt by myself and others that the material of the Symposium was of such value, in purely scientific and medical terms, that it merited publication. Accordingly, as Chairman of the Symposium, it has been my pleasure to prepare the proceedings in the form of an Acta Oto-laryngologica Supplement. As such, the proceedings are complete except for the full text of Professor Jongkees' paper and for the discussions following each paper. On the other hand I have added, retrospectively, a summary of the panel discussion with the intention of increasing its general value.

An accidental loss of the first and already carefully-edited transcript caused a considerable delay in publishing these proceedings. Nevertheless the material is considered to be of more than sufficient merit and value to warrant its publication now in spite of the delay.

As editor, I would like to record my thanks to the many persons who attended the Symposium and have subsequently helped this publication by careful preparation of the texts of their papers and/or by vetting of their contributions to the panel discussions which, inevitably, I had to edit heavily in order to convert it from colloquial to written expression.

Dr R. R. A. Coles
29th March 1972
University of Southampton, England

PREFACE

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Proceedings of the Symposium on Ménière's Syndrome Zandvoort September 3 1970

MENIERE'S — A SYNDROME OR DISEASE?

L. B W Jongkees

From the Wilhelmina Gasthuis, University of Amsterdam, The Netherlands

ABSTRACT

The name of Dr Prosper Ménière is connected with a syndrome consisting of cochlear vestibular and (para)-sympathetic symptoms. This syndrome indicates peripheral pathology It is unnecessary unwise, and misleading to use the name Ménière (with or without prefixes like para- or pseudo-) for vestibular pathology because in these cases the name Ménière indicates nothing but lack of knowledge.

Dr Ménière was also the first who described many causes of the syndrome that bears his name, especially those attacks of vertigo that seize the healthy patient, take away his forces, make him vomit, and strike him down until, after the period of sleep, he rises again, but for a slight deafness. It is a good habit to call this Ménière s disease.

Today we know that a hydrops labyrinthi is the anatomo-pathological substrate for Morbus Ménière, but we do not know what this hydrops really stands for neither do we know its genesis. For this reason the treatment of Ménière s disease is not yet based on solid ground.

ment of Ménière's disorder. These drugs include nicotonic acid, β-pyridyl carbinol, buphenine hydrochloride and cyclandelate, but none has been subject to a controlled clinical trial. However, this criticism cannot be levelled against the use of β-histine, the oral histamine analogue, which is β-(2-pyridyl) ethylmethylamine. Although criticised by Clemis (1969), this drug has been shown in at least two double-blind therapeutic trials (Elia, 1966; Hicks, Hicks & Cooley 1967) to be effective in the control of vertigo in Ménière's disorder. Moreover, apart from hydrochlorothiazide, it is the only method of treatment of Ménière's disorder which has been shown, in a double-blind study, to be more effective than a placebo in the control of the vertigo. The use of this histamine analogue seems rational when one considers Schayer's (1964) hypothesis that histamine is the intrinsic microcirculatory dilator. An alternative means of producing vasodilatation is by paralysis of the cervical sympathetic nerve (Passe & Seymour 1948). This paralysis may be produced temporarily by stellate ganglion block, which may also be used for treating acute attacks of the disorder (Wilmot, 1957), or permanently by cervicodorsal sympathectomy (Lewis, 1951; Wilmot, 1961, 1969). At the turn of the century G. Ferreri (1903) (quoted by Brunetti, 1934) resected both superior cervical sympathetic ganglia in a man with intractable tinnitus and the results were satisfactory and lasting. By means of the same operation, a quarter of a century ago, Mogan & Baumgartner (1945) abolished the vertigo and ameliorated the tinnitus in a patient who was subsequently shown to have Cogan's syndrome, so that it would appear that the indications for the operation, if accepted, are not confined to Ménière's disorder. However, Johnson (1954) considered that the results of the operation in Ménière's disorder were disappointing, and Strong (1957) reported that the success rate was less than 30 per cent. It may thus not be surprising that the operation was recently referred to as "an abandoned surgical technique for Ménière's disease" (Clemis, 1969). However, unlike the various operations upon the vestibular labyrinth which are designed to conserve hearing, but which sometimes damage it, this operation does not in itself at any time produce damage to residual hearing. Moreover, although hearing may not be improved, there is a one-third chance of a reduction in distortion and an intractable tinnitus may be relieved immediately. Sympathectomy we therefore find has a place in the management of bilateral disease, and where the hearing level is deteriorating despite medical measures, especially where dysacusis and troublesome tinnitus are conspicuous symptoms, but where patients are under the age of 55. Unfortunately, as Harrison & Naftalin (1968) point out, the results of stellate ganglion block seldom give any real helpful lead in the selection of cases for sympathectomy, and complications from injections into the region of the ganglion, by whichever route, are by no means rare and may be serious.

Table I. *Ménière's disorder: Treatment classification*

I	*Vasodilatation*		
	Pharmacological	–	Vasodilators
			Histaminics
	Surgical	–	Sympathectomy
II	*ACTH, corticosteroids*		
III	*Depression of vestibular response*		
	Reversible	–	Psychotropics
			Vestibular suppressives
	Irreversible	–	Streptomycin
			Vestibular neurotomy
IV	*Decompression*		
	Physico-chemical	–	Salt-and-water restriction
			Diuretics
			Topical osmotic
	Physical	–	Endolymphatic shunt
			-subarachnoid
			-otic-periotic
			Sacculotomy
			-non-repetitive (Fick)
			-repetitive (Cody)
			Utriculotomy
V	*Vestibular labyrinthine destruction*		
	Chemical	–	Alcohol injection
	Physical		
	Mechanical	–	Labyrinthectomy
	Thermal	–	Ultrasound
			Cryosurgery

Proceedings of the Symposium on Ménière's Syndrome Zandvoort September 3 1970

REVIEW OF TREATMENT OF MÉNIÈRE'S SYNDROME

R. Hinchcliffe

From the Institute of Laryngology and Otology University of London England

The treatment of a patient suffering from Ménière's syndrome is of course dependent upon which particular disease entity the patient is afflicted with. Ménière's syndrome is defined as a syndrome of paroxysmal attacks of vertigo in association with tinnitus and a gradually developing sensorineural hearing loss. A syndrome being a symptom-complex may cover a number of "disease entities" As well as including Ménière's disorder Ménière's syndrome may be due to a blood pigment autoimmune disorder (Vogt Koyanagi-Harada syndrome) polyarteritis nodosa (Cogan's syndrome) syphilis (late congenital) or trauma (perilymph leak) including that arising from operative intervention It may also occur secondary to pre-existing internal ear disease Excluding a perilymph leak which should be treated by tympanotomy and repair of the fistula of the fenestra ovalis, the various disease entities" should, for the most part be treated medically For a syphilitic Ménière's syndrome, ampicillin with or without corticosteroids, is indicated and the latter may also be the drug of choice for some of the other disease entities"

Ménière's disorder might well be termed the idiopathic Ménière's syndrome Mild cases or formes frustes" exist, where the triad of symptoms is incomplete Thus just as all cases of Ménière's syndrome are not cases of Ménière's disorder so all cases of Ménière's disorder may not be cases of Ménière's syndrome. Because of the incompleteness of the symptom complex in these formes frustes of Ménière's disorder they have sometimes been termed atypical or pseudo-Ménière's syndrome As Cawthorne & Hewlett (1954) and Jongkees (1964) have pointed out, many cases of Ménière's disorder respond to explanation and reassurance with or without psychotropic drugs. A five year longitudinal study of patients who were suffering from Ménière's disorder and who were treated conservatively showed no deterioration in their median hearing thresholds which could be attributed to the disorder (Hinchcliffe, 1970) Apart from therapeutic listening" the majority of the patients were receiving psychotropic drugs and were eventually able to discontinue their medication at some period or other during the period under review The most common drug was amylobarbitone and the next most common nortriptyline It is of interest that in a double blind clinical trial using doses of amylobarbitone higher than those used for the patients in the series, Reynolds Joyce, Swift Tovley and Weatherall (1965) showed that the drug was not significantly better than a placebo in the treatment of anxious outpatients. This placebo response should be borne in mind when considering the results reported for the treatment of Ménière's disorder with other methods which are classified in Table I

As Harrison & Naftalin (1968) point out the production of vasodilatation is a natural corollary to the belief that labyrinthine ischaemia is of importance in Ménière's disorder Thus a variety of vasodilator drugs have been used at one time or another in the treat

ment of Ménière's disorder. These drugs include nicotinic acid, β-pyridyl carbinol, buphenine hydrochloride and cyclandelate, but none has been subject to a controlled clinical trial. However, this criticism cannot be levelled against the use of β-histine, the oral histamine analogue, which is β-(2-pyridyl) ethylmethylamine. Although criticised by Clemis (1969), this drug has been shown in at least two double-blind therapeutic trials (Elia, 1966; Hicks, Hicks & Cooley, 1967) to be effective in the control of vertigo in Ménière's disorder. Moreover, apart from hydrochlorothiazide, it is the only method of treatment of Ménière's disorder which has been shown, in a double-blind study, to be more effective than a placebo in the control of the vertigo. The use of this histamine analogue seems rational when one considers Schayer's (1964) hypothesis that histamine is the intrinsic microcirculatory dilator. An alternative means of producing vasodilatation is by paralysis of the cervical sympathetic nerve (Passe & Seymour, 1948). This paralysis may be produced temporarily by stellate ganglion block, which may also be used for treating acute attacks of the disorder (Wilmot, 1957), or permanently by cervicodorsal sympathectomy (Lewis, 1951; Wilmot, 1961, 1969). At the turn of the century G. Ferreri (1903) (quoted by Brunetti, 1934) resected both superior cervical sympathetic ganglia in a man with intractable tinnitus and the results were satisfactory and lasting. By means of the same operation, a quarter of a century ago, Mogan & Baumgartner (1945) abolished the vertigo and ameliorated the tinnitus in a patient who was subsequently shown to have Cogan's syndrome, so that it would appear that the indications for the operation, if accepted, are not confined to Ménière's disorder. However, Johnson (1954) considered that the results of the operation in Ménière's disorder were disappointing, and Strong (1957) reported that the success rate was less than 30 per cent. It may thus not be surprising that the operation was recently referred to as "an abandoned surgical technique for Ménière's disease" (Clemis, 1969). However, unlike the various operations upon the vestibular labyrinth which are designed to conserve hearing, but which sometimes damage it, this operation does not in itself at any time produce damage to residual hearing. Moreover, although hearing may not be improved, there is a one-third chance of a reduction in distortion and an intractable tinnitus may be relieved immediately. Sympathectomy we therefore find has a place in the management of bilateral disease, and where the hearing level is deteriorating despite medical measures, especially where dysacusis and troublesome tinnitus are conspicuous symptoms, but where patients are under the age of 55. Unfortunately, as Harrison & Naftalin (1968) point out, the results of stellate ganglion block seldom give any real helpful lead in the selection of cases for sympathectomy, and complications from injections into the region of the ganglion, by whichever route, are by no means rare and may be serious.

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Goldman (1962) reported that 17 ketosteroid production is low in people with Ménière's disorder and that 90% of such patients show good response to injections of whole adrenal cortical extract, but not to corticotrophin which Maggio Perella & De Vita (1957) had previously found to be effective If Ménière's disorder is a psychosomatic disorder as Fowler & Zeckel (1952) and others contend or a manifestation of the adaptation syndrome then there should be a response to corticotrophin (Groen 1955) Of the two principal types of cortical steroids, i e. the glucocorticoids and the mineralocorticoids, there have been reports not only of the effectiveness of the glucocorticoids (Hauser 1959 Hirata 1963) but also claims for the administration of the mineralocorticoids (Naftalin & Harrison 1961). However according to Schayer's (1964) hypothesis, glucocorticoids, which previously had been shown to have a vasoconstrictor action by Ashton and Cook (1952) moderate the dilator action of histamine. Thus, in the sense that histamine and the glucocorticoids are essentially antagonistic in their action on the microcirculation, one would expect only one (if any) to be therapeutically effective in a microcirculatory disorder and the other compound to actually exacerbate symptoms. The influence of ACTH on patients with Ménière's disorder is, however complicated by the recent demonstration by Gejrot, Fluur & Levi (1966) that patients with Ménière's disorder along with other individuals who have sustained labyrinthine damage, react differently to psychological stress.

We have previously mentioned the effect of psychotropic drugs in ameliorating the symptoms in Ménière's disorder Of the more specific vestibular suppressives, those of the phenothiazine group e g cinnarizine and prochlorperazine appear to be the most effective In this section on "depression of vestibular response" we can for purposes of classification include both administration of streptomycin and vestibular neurotomy since both these procedures interrupt the flow of afferent impulses which signal to the brain the episodic disturbances of labyrinthine function The use of streptomycin depends on the specific vestibulo-toxic action of this antibiotic (Fowler 1948 Hamberger Hyden & Koch, 1949 Graybiel, Schuknecht, Fregly Miller & McLeod, 1967 Schuknecht, 1957) The drug is given in a dose of 1 g three times a day and its effect is monitored by daily caloric tests. The response of the affected ear or the more seriously affected ear if the condition is bilateral, disappears first, when treatment should be stopped Unfortunately compensation of equilibrium is less perfect with older patients. In any case compensation is never complete and all patients persist in having difficulty in walking in the dark (Graybiel et al. 1967) The use of the drug should therefore be confined to patients under the age of fifty years, where both ears are involved and where there has been no response to other medical treatment and where the patient refuses to undergo operation

Vestibular neurotomy has now been used for over forty years and, of the 278 cases operated on by Dandy Green (1959) reported that the vertigo was relieved or improved in 95% of cases but in nearly two-thirds of the cases, the hearing got worse and in 14% of cases the patient eventually became deaf" Tinnitus was reported relieved in 50% of cases. However other series of cases have shown less success (Putnam 1938 Walsh & Adson, 1940) A Canadian series showed that, although the immediate results were good the final results were usually disappointing (Ireland 1949) In many cases the hearing has continued to fall away Moreover it should be remembered that this entails an intracranial operation which is not without risk. The risk, however may be slight Only two of Dandy's patients died, and here the death was due to meningitis which would now be expected to respond to current methods of treatment

Even before Hallpike & Cairns (1938) had demonstrated endolymphatic hydrops as the histological correlate of Ménière's disorder

Mygind (1926) had suggested that alterations in body fluids may play a part in the pathogenesis of Ménière's disorder. There are individual patients whose episodes of vertigo respond to salt and fluid restriction and, using a double-blind technique, Klockhoff & Lindblom (1966) showed that hydrochlorothiazide is beneficial with respect to the hearing loss, vertigo and general condition in Ménière's disorder. The modus operandi for water and salt depletion procedures is uncertain since Perlman, Golding & Cales (1953) failed to demonstrate any consistent effect by either water depletion and loading or salt depletion and loading in cases of Ménière's disorder. Harrison & Naftalin (1968) have shown that the acute attacks of vertigo occur during a phase of sodium diuresis concomitant with a water gain.

A century ago, Knapp (1871) suggested that Ménière's disorder might be analogous to glaucoma and the symptoms be due to increased intralabyrinthine fluid pressure. Portmann, Sr. (1927) followed up this suggestion 55 years later by treating Ménière's disorder by making an opening into the endolymphatic sac. He subsequently performed 60 operations of this type over the subsequent 38 years. In this series, the vertigo was relieved in 93% of cases and the tinnitus and the hearing improved each in about one-third of cases. Thus, so far as the vertigo and the hearing are concerned, Portmann obtained better results than House (1965) obtained for his 243 cases treated with the subarachnoid endolymphatic shunt operation, where the vertigo was said to be improved in three-quarters of the cases and the hearing in 10% only. It is therefore not surprising that Portmann, Jr. (1969) should say: "It seems useless to place a tube in the arachnoidal spaces as proposed by House—a simple opening is sufficient to provoke improvement." Moreover, Shambaugh (1966) found that he could obtain the same results with simple exposure of the sac. With such a dummy operation, what could have been better as a control trial to assess the results of the subarachnoid endolymphatic shunt operation? Furthermore, 3 years later Shambaugh (1969) wrote: "My initial enthusiasm for operating upon the endolymphatic sac to improve hearing in Ménière's disorder has steadily cooled. Only once did I duplicate the dramatic success of the first case with return of normal hearing and in only two more cases was there a significant, but not great, improvement of hearing. In all the rest, i.e. 92 per cent of cases, the hearing was unchanged or worse. Insertion of the "teflon" film did not give any better results in my hands than simple decompression." The operation may be complicated by otitic hydrocephalus or meningitis, so that it is not free from hazard. A simpler method of depressing the membranous labyrinth has been devised by Fick (1964), who perforates the centre of the stapes base with a needle. This opening is then enlarged to 1 mm with a burr, more fluid drawn out of the labyrinth, and the mucosa replaced. Although the earlier results for this operation were reported to be very good (relief of vertigo in 90% of cases and improvement in hearing in 65% of cases) the late results have been less good. As Portmann (1969) pointed out, the results obtained by other surgeons who experimented with the procedure are bad and deafness is frequent following the operation. Cody, Simonton & Hallberg (1967) have endeavoured, ingeniously, to improve on this operation by inserting a small prosthesis, shaped like a tin-tack, in the fistula opening so that the saccule is punctured each time it seals and subsequently distends again, a procedure which they term automatic repetitive decompression of the saccule. Frequently, though, the dilated terminal end of the cochlear duct, and not the saccule, is attached to the stapes base which might provide an anatomical explanation for differences in results on different patients. Moreover, the tack sacculotomy may itself produce a Ménière's syndrome due to the creation of a perilymph fistula (Pulec, 1969). Furthermore, the histopathological picture of endolymphatic hydrops is the end-result and not the cause of Ménière's disorder (Neumann,

Goldman (1962) reported that 17 ketosteroid production is low in people with Ménière s disorder and that 90% of such patients show good response to injections of whole adrenal cortical extract but not to corticotrophin which Maggio Perella & De Vita (1957) had previously found to be effective If Ménière s disorder is a psychosomatic disorder as Fowler & Zeckel (1952) and others contend or a manifestation of the adaptation syndrome then there should be a response to corticotrophin (Groen, 1955) Of the two principal types of cortical steroids, i e the glucocorticoids and the mineralocorticoids, there have been reports not only of the effectiveness of the glucocorticoids (Hauser 1959 Hirata 1963) but also claims for the administration of the mineralocorticoids (Naftalin & Harrison 1961) However according to Schayer s (1964) hypothesis, glucocorticoids, which previously had been shown to have a vasoconstrictor action by Ashton and Cook (1952) moderate the dilator action of histamine Thus, in the sense that histamine and the glucocorticoids are essentially antagonistic in their action on the microcirculation one would expect only one (if any) to be therapeutically effective in a microcirculatory disorder· and the other compound to actually exacerbate symptoms. The influence of ACTH on patients with Ménière s disorder is, however complicated by the recent demonstration by Gejrot, Fluur & Levi (1966) that patients with Ménière s disorder along with other individuals who have sustained labyrinthine damage react differently to psychological stress.

We have previously mentioned the effect of psychotropic drugs in ameliorating the symptoms in Ménière s disorder Of the more specific vestibular suppressives those of the phenothiazine group e g cinnarizine and prochlorperazine appear to be the most effective In this section on depression of vestibular response" we can for purposes of classification, include both administration of streptomycin and vestibular neurotomy since both these procedures interrupt the flow of afferent impulses which signal to the brain the episodic disturbances of labyrinthine function The use of streptomycin depends on the specific vestibulo-toxic action of this antibiotic (Fowler 1948 Hamberger Hyden & Koch 1949 Graybiel Schuknecht Fregly Miller & McLeod, 1967 Schuknecht, 1957) The drug is given in a dose of 1 g three times a day and its effect is monitored by daily caloric tests. The response of the affected ear or the more seriously affected ear if the condition is bilateral disappears first when treatment should be stopped Unfortunately compensation of equilibrium is less perfect with older patients In any case compensation is never complete and all patients persist in having difficulty in walking in the dark (Graybiel et al. 1967) The use of the drug should therefore be confined to patients under the age of fifty years, where both ears are involved and where there has been no response to other medical treatment and where the patient refuses to undergo operation

Vestibular neurotomy has now been used for over forty years and of the 278 cases operated on by Dandy Green (1959) reported that the vertigo was relieved or improved in 95% of cases but in nearly two-thirds of the cases, the hearing got worse, and in 14% of cases the patient "eventually became deaf" Tinnitus was reported relieved in 50% of cases. However other series of cases have shown less success (Putnam 1938 Walsh & Adson 1940). A Canadian series showed that although the immediate results were good the final results were usually disappointing (Ireland 1949) In many cases the hearing has continued to fall away Moreover it should be remembered that this entails an intracranial operation which is not without risk The risk however may be slight Only two of Dandy s patients died and here the death was due to meningitis which would now be expected to respond to current methods of treatment

Even before Hallpike & Cairns (1938) had demonstrated endolymphatic hydrops as the histological correlate of Ménière s disorder

Mygind (1926) had suggested that alterations in body fluids may play a part in the pathogenesis of Ménière's disorder. There are individual patients whose episodes of vertigo respond to salt and fluid restriction and, using a double-blind technique, Klockhoff & Lindblom (1966) showed that hydrochlorothiazide is beneficial with respect to the hearing loss, vertigo and general condition in Ménière's disorder. The modus operandi for water and salt depletion procedures is uncertain since Perlman, Golding & Cales (1953) failed to demonstrate any consistent effect by either water depletion and loading or salt depletion and loading in cases of Ménière's disorder. Harrison & Naftalin (1968) have shown that the acute attacks of vertigo occur during a phase of sodium diuresis concomitant with a water gain.

A century ago, Knapp (1871) suggested that Ménière's disorder might be analogous to glaucoma and the symptoms be due to increased intralabyrinthine fluid pressure. Portmann, Sr (1927) followed up this suggestion 55 years later by treating Ménière's disorder by making an opening into the endolymphatic sac. He subsequently performed 60 operations of this type over the subsequent 38 years. In this series, the vertigo was relieved in 93% of cases and the tinnitus and the hearing improved each in about one-third of cases. Thus, so far as the vertigo and the hearing are concerned, Portmann obtained better results than House (1965) obtained for his 243 cases treated with the subarachnoid endolympathic shunt operation, where the vertigo was said to be improved in three-quarters of the cases and the hearing in 10% only. It is therefore not surprising that Portmann, Jr (1969) should say: "It seems useless to place a tube in the arachnoidal spaces as proposed by House—a simple opening is sufficient to provoke improvement." Moreover Shambaugh (1966) found that he could obtain the same results with simple exposure of the sac. With such a dummy operation, what could have been better as a control trial to assess the results of the subarachnoid endolymphatic shunt operation? Furthermore, 3 years later Shambaugh (1969) wrote: "My initial enthusiasm for operating upon the endolymphatic sac to improve hearing in Ménière's disorder has steadily cooled. Only once did I duplicate the dramatic success of the first case with return of normal hearing and in only two more cases was there a significant, but not great, improvement of hearing. In all the rest, i.e. 92 per cent of cases, the hearing was unchanged or worse. Insertion of the "teflon" film did not give any better results in my hands than simple decompression." The operation may be complicated by otitic hydrocephalus or meningitis, so that it is not free from hazard. A simpler method of depressing the membranous labyrinth has been devised by Fick (1964), who perforates the centre of the stapes base with a needle. This opening is then enlarged to 1 mm with a burr, more fluid drawn out of the labyrinth, and the mucosa replaced. Although the earlier results for this operation were reported to be very good (relief of vertigo in 90% of cases and improvement in hearing in 65% of cases) the late results have been less good. As Portmann (1969) pointed out, the results obtained by other surgeons who experimented with the procedure are bad and deafness is frequent following the operation. Cody, Simonton & Hallberg (1967) have endeavoured, ingeniously, to improve on this operation by inserting a small prosthesis, shaped like a tin-tack, in the fistula opening so that the saccule is punctured each time it seals and subsequently distends again, a procedure which they term automatic repetitive decompression of the saccule. Frequently though, the dilated terminal end of the cochlear duct, and not the saccule, is attached to the stapes base which might provide an anatomical explanation for differences in results on different patients. Moreover, the tack sacculotomy may itself produce a Ménière's syndrome due to the creation of a perilymph fistula (Pulec, 1969). Furthermore, the histopathological picture of endolymphatic hydrops is the end-result and not the cause of Ménière's disorder (Neumann,

1964) The histological picture of endolymphatic hydrops may be absent in cases where there has been clinical evidence for Ménière s disorder (Berggren 1949 Wustrow & Borkowsky 1960)

In the small percentage of cases of Ménière s disorder where medical treatment has failed and recourse must be had to surgery the hearing in the affected ear is usually so impaired that one need not attempt to conserve it Moreover there may be so much distortion and tinnitus that the patient wishes the remaining auditory function to be destroyed. In these cases, membranous labyrinthectomy (Cawthorne 1943) is the method of choice However in the few cases where intractable vertigo is unresponsive to medical treatment and yet there is useful auditory function in the involved ear then destruction of the vestibular labyrinth only may be attempted by either ultrasound (Arslan 1962 James, 1965) or cryosurgery (House 1966 Wolfson Cutt Ishiyama & Myers, 1968) Although the principle of ultrasonic therapy is based on the selective destruction of the vestibular neuroepithelium it is now thought to exert also some beneficial action on the hydrodynamics of the endolymphatic system (James, Freundlich Buller Wells & Williams 1964) There is an alteration in the electrolyte composition of the endolymph The potassium concentrate is reduced and the sodium is increased Shrinkage of both the utricle and saccule have been observed suggesting a reduction in endolymph pressure House (1969) thinks that ultrasound might destroy the membranous labyrinthine wall producing an otic-periotic fistula

Using a 3 megacycle cone having a maximum power output of 22 watts per cm² Angell James (1969) has been able to stop the vertigo in 85% of a series of more than 200 cases, and the tinnitus in 30% of these cases. The hearing was impaired by 10 dB or more in 44% of cases, including complete loss in 2% Thus, as Angell James himself points out there can be few other surgical measures that can offer such a satisfactory prospect for these unhappy patients. A facial palsy occurred in under 1% of cases and in no individual was this permanent.

Some Reflections on a "Histamine Hypothesis"

In view of the confirmed demonstration that an oral histamine analogue has a beneficial effect upon Ménière s disorder it behoves us to consider whether some of the diverse features of Ménière s disorder might not be explained on a histamine hypothesis. There are fifteen features that I would wish to consider

(1) There is evidence that Ménière s disorder is a psychosomatic one (Fowler & Zeckel, 1952 1953 Ceroni & Franzoni 1963 Jongkees, 1963 Siirala, Siltala & Lumio 1965 Hinchcliffe 1967 *a*)

(2) There is a connection between migraine and Ménière s disorder (Matzdorff 1936 Atkinson 1962 Hinchcliffe 1967 *b*)

(3) Gastro-duodenal lesions may be associated with Ménière s disorder including the simultaneous occurrence of exacerbations (Wyburn Mason 1959)

(4) There may be pre-existing or co-existing internal ear pathology other than hydrops.

(5) The average duration in between episodes of vertigo is one week

(6) Stimulation of the sympathetic nervous system may produce changes suggestive of Ménière s disorder (Seymour & Tappin 1953)

(7) Acute attacks are associated with an increase in the plasma potassium concentration (Talbott & Brown 1940 Clayton Birch & Hughes 1962)

(8) Anti-histamines, e g promethazine may give prompt and persisting relief (Korkis, 1958)

(9) As well as promethazine other phenothiazine drugs which exhibit less anti histamine activity provide relief from symptoms in Ménière s disorder e g. prochlorperazine and cinnarizine

(10) Haloperidol has been reported to cause complete disappearance of vertiginous attacks in Ménière s disorder (Cunego & Citterio 1963)

(11) Ménière s disorder responds to the anti-motion sickness drugs, such as dimenhydrinate.

(12) Some patients respond to a low salt and water diet.

(13) Tonsillectomy has been reported to produce relief of symptoms.

(14) Cases of Ménière s disorder due to an allergy in particular food allergy have been reported (Clemis, 1969 Eagle, 1948).

(15) Individuals suffering from mastocytosis or myelogenous leukemia may suffer from vertigo.

A histamine effect might be suggested for each of these fifteen points, and this might provide a unifying concept specifically

(1) Emotional stress may result in histamine liberation. In the brain, the highest concentrations of histamine are found in the hypothalamus, which provides the anatomical basis for the physiological correlates of emotional activity

(2) Horton s (1941) histamine headache is now considered to be identical with periodic migrainous neuralgia, which may be considered a migraine variant. In migraine itself there is evidence for the release of serotonin, a vaso-active amine related to histamine (Sicuteri, Testi & Anselmi, 1961 Curzon, Theaker & Phillips, 1966).

(3) In experimental animals, histamine provides a potent means of producing peptic ulceration

(4) Tissue injury not only leads to the release of histamine but also stimulates production (Dekanski, 1945)

(5) A weekly cycle could be based on antigen-antibody reactions, as well as the suggested psychosomatic determinants. In any case there is a psychosomatic-allergy interaction. Kourilsky has reported, regarding asthmatic crises, that they were always preceded by anxieties. Suppression of the emotional stimulus suppressed the allergic manifestations. Antigen-antibody reactions release histamine.

(6) Histamine acts not only on the peripheral ganglion cells of the sympathetic system, but exerts a direct action on the central ganglion cells of the system as well (Trendelenburg, 1956).

(7) Intravenous injection of histamine in the cat produces a sharp rise in plasma potassium concentration (Macmillan & Vane, 1956)

(8) A response to anti-histamine would be plausible if Ménière s disorder were in some way due to histamine liberation.

(9) Most of the phenothiazines are histamine antagonists.

(10) Although the chemical structure of haloperidol resembles that of pethidine the pharmacological activity is similar to the piperazine substituted phenothiazines.

(11) Although the anti-motion sickness effect of the antihistaminics is said to be unrelated to histamine antagonism, it may well, in fact, be due to this antagonism, but reflecting the specificity of "histamine receptors" in the central nervous system.

(12) The low salt and water" diet, being a cheese and protein elimination diet might also be considered to be a low histidine diet. Since histidine is a histamine-precursor such a diet should decrease the histamine in the body

(13) The histamine content of tonsils is reported to be higher than that of any other organ (Lorenz, Heitland, Werle, Schauer & Gastpar 1968).

(14) The occurrence of an allergy implies an antigen-antibody reaction and this releases histamine (Humphrey & Jaques, 1953)

(15) Mastocytosis and myelogenous leukaemia are the two conditions in which there is an abnormally high production of histamine

It might therefore be contended that many phenomena associated with Ménière s disorder or Ménière s syndrome might be explained on the basis of an increased histamine production or of a sensitivity to histamine. It thus behoves us to ascertain whether we might be administering β-histine for the wrong reasons, i.e. not as a vaso-dilator but as a method of de sensitising to histamine This suggestion, however might be questioned on the grounds that

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tolerance to histamine is said not to increase even after prolonged courses of desensitisation (Wells, Gray & Dragstedt 1941 Feinberg 1946) Perhaps this may apply only to certain physiological effects of histamine and not those to a susceptible or damaged organ in this case the ear Although there is evidence that it is a more generalised disorder the thesis of Locus minoris resistentiae is suggested to explain the apparent localisation of Ménière s disorder in the ear

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hahns, Raynaud' phenomenon and acrocyanosis (in the women) were common. In addition in most of the patients there seemed clear evidence to support Hinchcliffe (1967 *b, c*) that psycho-somatic factors play a part in the aetiology of this condition.

I each case the hearing loss was purely neuro-sensory in type, was associated with positiv recruitment, with relatively good speech reception and with completely *normal* middle ear and Eustachian tube function. The attacks were not related to upper respiratory tract infection. A caref l assessment of the hearing was performed both before and after treatment. As it is seldom possible to alter neuro-sensory hearing loss in this or other conditions above the frequency of 1 000 Hz we decided to limit our study to the three frequencies 250 500 and 1 000 Hz which ere represented as an average decibel loss.

Vestibular testing consisted of estibular analysis consisting of clinical balance tests, positional tests, optokinetic tests, caloric tests, nd a full series of acceleratory and deceleratory rotation tests. The findings in all cases were consistent with the auditory localisation findings and followed the pattern which e expect in case of Ménière's disease. Thus clinical balance was normal between attacks, and positional test ere negative. Optokinetic nystagmus was symmetrical and normal except in those cases where there as definite preponderance to one side. I these cases the optokinetic nystagmus showed slight preponderance in the same direction. Caloric tests gave typical Menière-like reactions and rotation tests gav the reduced amplitude rather constant speed nystagmus hich will be described in greater detail elsewhere.

For the purpose of this study however w have limited our enquiry into the effect of betahistine hydrochloride upon hree pure tone hearing levels and upon the nystagmus recorded from *three* different rates of acceleration and one rate of deceleration. The former consist of 1 sec² 3 sec and 6 /sec² and the latter 90° sec².

The acceleration tests provide 90 sec of stimulus recording time in the 1 sec² test, 30 sec stimulus recording thre in the 3 sec² test 15 sec stimulus recording time in the 6 sec² test and in the 90° sec² deceleration test the nystagmus is a post stimulatory effect, and usually lasts for approximately 40 sec ith the nystagmus steadily declining from onset to the end of reaction.

The acceleratory and deceleratory tests are performed to both right and left giving a total of 6 accelerations and 2 decelerations to be studied. The paper speed used has been 1 25 cm sec and pen deflections hav been previously calibrated to known eye movements.

The assessment is based upon the eye shift in degrees per second related to each stimulus and this assessment has been made both before and after completing treatment for each individual stimulus.

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In the acceleratory tests we have considered the eye shift per second in the first 15 sec following the stimulus. T detect differences inherent in an increased latency period (start-lag) we have subdivided this into two periods of 1 5 sec and 6-15 sec in-clush As these tw estimations are done on 3 clock ise and 3 anti clockwise rotations we have a total of 12 calculations for each set of acceleratory rotation tests per subject.

In the 2 deceleratory tests the calculation has been confined to the initial 5 sec only of recording (latency period is unimportant after such a powerful stimulus) so that w hav only 2 calculations per set of rotation tests per subject.

T ble I show the method adopted to study these calculations.

Table I

	Eye shift/sec			
	Left		Right	
	0-5	6-15	0-5	6-15
Accelerations				
1 /sec²				
3 /sec²				
6 /sec²				
Deceleration				
90 /sec				

Drug dosage

All patients in this study after initial auditory and vestibular analysis ere given betahistine hydrochloride 8 mg t d (I 24 mg daily) for a period of 3 months N other drug as given during this period. All patients took their tablets regularly and there were no side effects. Post treatment analysis was performed just before treatment had been completed.

RESULTS

In Table II is summarised the results of treatment on hearing. For both ears the hearing loss after treatment was less than before treatment but the difference although suggestive is not statistically significant as in the left ear there was a one in ten possibility that the improvement was due to chance.

In Table III the vestibular function tests before and after treatment are summarised. It

THE EFFECT OF BETAHISTINE HYDROCHLORIDE IN MÉNIÈRE'S DISEASE

T J Wilmot

From the Department of Otolaryngology Tyrone County Hospital Omagh Northern Ireland

INTRODUCTION

Objective assessment of vestibular function can only be achieved with highly sophisticated methods. It is desirable first to localise the lesion as central or peripheral and second to be able to measure function in an accurate and repeatable manner

For the localisation of lesions affecting balance and hearing a system of auditory analysis is essential Pure tone audiometry is used to assess the thresholds of air and bone conduction hearing to measure the loudness discomfort level, to perform the Fowler s binaural loudness balance test (if appropriate) to register the SISI scores, to measure tone decay and to show the difference between the cochlear response to interrupted and continuous tones. These measures will confirm the presence of neuro-sensory deafness and will determine the degree of pure tone loss of hearing the presence or absence of recruitment and will give a definite indication as to whether the hearing loss is cochlear or retrocochlear

Speech audiometry should give results consistent with the pure tone findings Where recruitment is present it is common to find relatively good speech perception with adequate amplification Where recruitment is absent and there is excessive pure tone decay speech discrimination is very poor

In a case where the middle ear and Eustachian tube function is suspect acoustic impedance audiometry will clarify the position and help to differentiate the relative importance of the conductive and neuro-sensory components present in the total hearing loss.

We have therefore in all these measures, the ability to localise with some accuracy the site of the lesion affecting hearing We can also assume in the vast majority of cases that the vestibular lesion is likely to be peripheral or central in keeping with the cochlear lesion.

Our next task is to establish reliable and repeatable vestibular function tests and to portray the results of these tests in a representative and statistically significant manner

Our equipment and testing methods have been described previously (Dittrich & Allen 1965 Dittrich & Wilmot 1965 Wilmot & Allen 1965 Wilmot 1966) In our latest communication (Wilmot, in press) we support the use of the "average eye shift per second" advocated by Linthicum & Churchill (1968) as a reliable means of representing induced nystagmic eye movements. In this paper in addition to the hearing, we have studied this factor as representative of vestibular function, in a small group of patients before and after treatment

CLINICAL MATERIAL AND METHODS

The small number of patients for this study were very carefully selected from a much larger group complaining of deafness, tinnitus and vertigo In each case they had a history of episodic rotatory vertigo tinnitus and hearing loss Nausea and vomiting with the attacks, a sensation of fullness in the ear between attacks, and an associated history of migraine chil

bition, Raynaud' phenomenon and acrocyanosis (in the women) were common. In addition in most of the patients there seemed clear evidence to support Hinchcliffe (1967 *a, b, c*) that psycho-somatic factors play a part in the aetiology of this condition.

I each case the hearing loss was purely neuro-sensory in type, was associated with positive recruit ment, with relatively good speech reception and with completely *normal* middle ear and Eustachian tube function. The attacks were not related to upper respiratory tract infection. *A careful assessment of the* hearing was performed both before and after treat ment. As it is seldom possible to alter neuro-sensory hearing loss in this or other conditions abov the frequency of 1 000 Hz we decided to limit our study to the three frequencies 250, 500 and 1 000 Hz which *ere represented as an average decibel loss.*

Vestibular testing consisted of vestibular analysis consisting of clinical balance tests, positional tests, optokinetic tests, caloric tests, and full series of acceleratory and deceleratory rotation tests. The findings in all cases were consistent with the auditory localisation findings and followed the pattern which expect in case of Ménière's disease. Thus clinical balance was normal between attacks, and positional tests ere negative. Optokinetic nystagmus was ym metrical and normal except in those cases where there was definite preponderance to one side. In these cases the optokinetic nystagmus showed slight preponderance in the same direction. Caloric test gave typical Ménière-like reactions and rotation tests gave the reduced amplitude rather constant speed nystagmus which will be describing in greater detail elsewhere.

For the purpose of this study however we have *limited our enquiry into the effect of betahistine* hydrochloride upon *three* pure tone hearing levels and upon the nystagmus recorded from *three different* rates of acceleration and *one* rate of deceleration. The former consist of 1 /sec² 3 sec² and 6 /sec² and the latter 90° sec².

The acceleration tests provide 90 sec of stimulus recording time in the 1 sec² test, 30 sec stimulus recording time in the 3 sec² test, 15 sec stimulus recording time in the 6 sec² test and in the 90°/sec² deceleration test the nystagmus is post stimulatory effect, and usually lasts for pproximately 40 sec with the nystagmus steadily declining from onset to *the end of reaction.*

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Table II

Mean hearing level (dB)	Pre-drug			Post-drug			
	Mean	S E.	No of patients	Mean	S.E.	No. of patients	P*
Left ear	29.5	5 6.	11	18 8	5.59	11	0.10
Right ear	15 0	8 17	11	11 8	6.84	11	>0.10

Using Wilcoxon s signal rank test.

will be seen that at all rates of acceleration and deceleration there is an increase in the mean eye shift/sec At certain rates of acceleration and with deceleration this increase is statis tically significant

Subjectively 9 out of 11 patients claimed an improvement in the symptom of vertigo and all 11 claimed reduction in tinnitus.

COMMENT

Treatment with betahistine hydrochloride (Serc) was associated with changes in the symptoms of all patients, and with changes in the vestibular function tests

Comparison of the 22 post treatment audiographs with the 22 pre treatment audiographs demonstrates that in 10 there was an improve ment of hearing after treatment in 9 there was no change and in 3 the hearing deter iorated There was an overall average gain in hearing over the whole group in both ears.

Rotary stimulation produced more pronounced nystagmus following treatment than present initially In view of the reduced nystagmus commonly present to rotatory stimuli in this condition it is suggestive that betahistine hydrochloride has improved vestibular function in keeping with the subjective im pression of the patients.

Table III *The vestibular function tests before and after Serc*

Response	Pre-Serc			Post-Serc			
	Mean	S E.	No. of pats.	Mean	S E.	No of pats.	P*
In first 0–5 sec							
1 /sec² Left	.3	0 40	10	3 0	0.49	10	>0 10
1 /sec² Right	11 7	0 28	10	3.2	0 49	10	0 02
3 /sec² Left	3 7	0.50	10	4 8	0 44	10	0 05
3 /sec² Right	3 7	0 82	10	4 9	0.74	10	0.10
6 /sec² Left	6 6	1 45	10	8 9	1.20	10	>0 10
6°/sec² Right	5 4	0 98	10	9 0	1 61	10	0 0.
In 6–15 sec							
1 /sec² Left	2.9	0 46	10	3 1	0 50	10	0 10
1 /sec² Right	2 3	0 42	10	4 0	0 60	10	0 01
3 /sec² Left	5 8	0 90	10	7 7	1 35	10	0 10
3 /sec² Right	5 7	1 18	10	8.0	1 40	10	0 0.
6 /sec² Left	9 9	1 83	10	12.5	1 42	10	>0 10
6°/sec² Right	8 7	2 10	10	13 8	59	10	0 0.
90°/sec² Left	18.2	2 87	10	23 4	4 57	10	>0 1
90°/sec² Right	20 3	4 05	10	24 1	4 00	10	>0 1

Using Wilcoxon's s gnal rank test

ACKNOWLEDGEMENTS

I wish to express my thanks to Dr Michael Flynn for supplying me with betahistine hydrochloride for clinical trial and to him and his colleagues of the Clinical Research Department, Philips-Duphar Weesp, Holland, for their collaboration and statistical help

The estimation of average eye shift per second was performed by Mr R. H. Allen, my Chief Technician, to his usual high standard. Mr Allen was also responsible for the auditory and vestibular testing involved.

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METABOLITES OF SERC AND INTERACTION OF SERC WITH ANTIHISTAMINES

H McKennis Jr

From the Department of Pharmacology Medical College of Virginia, Richmond Virginia USA

Serc[1] (2-(2 methylaminoethylpyridine dihydrochloride)) which is marketed in the United States under the generic name of betahistine hydrochloride first became an eagerly sought drug primarily through the efforts of Bayord T Horton of the Mayo Clinic. The compound was synthesized by Löffler in 1904 and was neglected until 1941 when Walter Hunt & Fossbinder restudied the synthesis of the compound and compared it (Hunt & Fossbinder 1942) with a number of related pyridylalkylamines for possible sympathomimetic activity Contrary to many expectations which were based upon a review of Hartung (1931) the 2-(2-pyridyl)alkylamines in the investigated series showed a physiological activity similar to histamine and a lack of sympathomimetic activity The structural resemblances between histamine and Serc were early recognized by Fossbinder and his co-workers by comparing flat, two-dimensional representations of the molecules the similarity in structure is even more striking when molecular models are compared

When the first commercial supplies of Serc, then known as PT 9 and related compounds became available to Horton he initiated basic pharmacological and clinical studies with these materials (Horton & Macy 1946 Horton, 1961 Horton & Von Leden 1962 Horton, 1962) Horton s interests were broad He recognized the possible beneficial effects of Serc in many disorders, including Ménière s syndrome However the main thrust of his work was to treat a peculiar unilateral type of headache called histaminic cephalgia, although it differs from the usual bilateral headache that can be induced with histamine The unilateral headache (Horton s syndrome) which often brings with it suicidal tendencies, is totally incapacitating to the patient at the height of the attacks. These can occur in the daytime or after the patient has retired The meticulous work of Horton and his collaborators over a period of years produced data on an extensive series of cases in which patients with Horton s syndrome were returned to a productive life by means of treatment with Serc.

Concurrent with the studies on Horton s headache at the Mayo Clinic preliminary observations were made on the use of Serc in a variety of vascular disorders, based upon the premise that Serc has some rather specific histamine like qualities and that much of its useful pharmacological activity resides in ability to increase the passage of blood through the microcirculation thus aiding in the restoration or maintenance of normal physiological function. One chance observation, yet to be fully exploited in the treatment of one patient suffering from both Horton s syndrome and angina pectoris deals with the spectacular recovery of the patient from the incapacitating effects of both afflictions. Observations on this patient over a period of 6 months were faithfully recorded by Horton and Dathe

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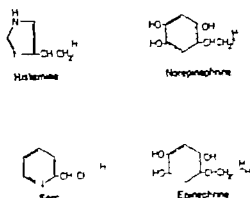


Fig. 1

The long history of need for a satisfactory general regimen for the control of Ménière's syndrome created many clinical studies on the use of Serc. To date, the application to Ménière's disease has probably attracted more attention than all the other varied usages combined. Since it is the interest in Ménière's syndrome that has brought about the organization of this meeting, mention should be made of the many early clinical papers.[*] Papers on the program today include the work of a wide international distribution of investigators.

Our own work on the metabolism of Serc has been directed primarily towards identification of metabolites of Serc and the role of these and other compounds in controlling or terminating pharmacological responses to the parent Serc. In the recounting of some of these studies, I wish to acknowledge gratefully the collaboration of Dr Herlbert Konzett, who has been serving as Visiting Professor of Pharmacology at the Medical College of Virginia, while on leave from his post at the University of Vienna. Dr Edward R. Bowman and Dr Faye J. Bowman, who incidentally are not related, have performed many of the chemical studies, while Mr Robert G. Bost diligently pursued both chemical and biological aspects of the problem.

The problem of the metabolism of Serc becomes all the more intriguing when one examines its structure (Fig. 1) in comparison with those of epinephrine, norepinephrine and histamine. From this one can easily see why at first glance, Hunt & Fosbinder originally thought that Serc might have some epinephrine-like qualities. As it turned out, Serc resembles histamine more in its physiological characteristics, and indeed the work of Baez (1969), Baez, Lorenzo & Orkin (1970), and Martinez (1972) has shown that Serc in its action in opening up the microcirculation is opposed by the constrictor effect of norepinephrine.

Once Serc has entered the body a number of different processes, including metabolism, become available for its elimination. From chemical structural considerations, either monoamine oxidase or histaminase might be considered logical catalysts for oxidation of the side chain of Serc. Based upon the close structural resemblance between Serc and histamine, Werle and Palm (1953) studied the effect of a histaminase or diamineoxidase preparation from peas on the two compounds. As adjudged by oxygen uptake, Serc was virtually unaffected by the enzyme preparation. Additionally Serc inhibited the oxidation of histamine. Werle & Palm also showed that Serc and 2-(2-aminoethyl)pyridine (demethyl Serc) had a histamine-like action on isolated strips of gut. This effect was blocked by the antihistaminic antazoline. Latter studies showing similar effects of Serc and 2-(2-aminoethyl)pyridine on isolated strips of gut were reported by Ariëns & Simonis (1960). In our current studies on Serc, attention has been directed to possible mammalian metabolic changes in the side chain of the molecule and the possible role of these events in controlling pharmacological responses in sub-human species.

Metabolism of Serc in rabbits

Dutch female rabbits in the studies (Bowman, Bowman & McKennis, 1970 *a*, *b*) received 2-(2-methylaminoethyl)pyridine ("Serc base"), which was administered as a single dose (100 mg/kg). The urine was collected from animals

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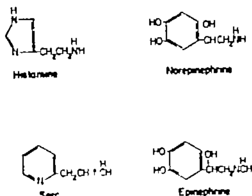


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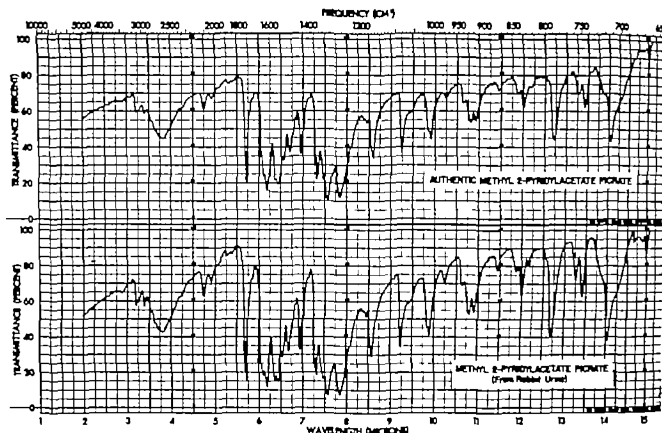


Fig 2 Comparison (in KBr pellet) of the infrared spectra of authentic methyl 2-pyridylacetate picrate and specimen prepared from 2 pyridylacetate from the metabolism of Serc.

during the subsequent 48-hour period. The method for preliminary analysis of the urine is relatively simple and depends essentially upon a separation of metabolites into groups, depending upon their acidic basic or neutral behavior

In a typical experiment with rabbits, the urine from 6 animals (approx. 2 kg each) was pooled. After clarification with diatomaceous earth the urine was passed onto a column of Dowex 50 H which retains or retards acidic and basic metabolites of Serc in which the pyridine ring is intact. The column effluent and water washes did not give a positive Koenig test for pyridine compounds and were discarded The column was then eluted with 5 N ammonium hydroxide which displaced both amphoteric and basic components, including any unchanged Serc, which might be present Previous studies with other pyridine compounds have indicated (McKennis, Turnbull & Bowman 1963) that many quaternary ammonium compounds formed by the biological N methylation of the pyridine ring can be removed from the column for later investigation by washing the column well with hydrochloric acid

A preliminary investigation of the ammoniacal eluate based upon UV absorption at 263 nm suggested that approximately 95% of the administered Serc was present in this fraction in some form or other This result was indicative of rather effective elimination of the drug by urinary excretion and led us to examine the urine further The ammoniacal solution was then placed upon a column of Dowex 21 K (OH) The effluent and water wash from this column on the basis of ultra violet absorption and thin layer chromatography contained at the most only trace quantities of basic pyridine compounds, which would include unchanged Serc, and possible basic metabolites, such as 2 pyridylethanol 2-(2-aminoethyl)pyridine and 2-pyridylacetal-

dehyde. A rather effective metabolism of Serc to other material, mainly acidic in nature, in the rabbit was thus indicated.

The Dowex 21 K (OH) column was then exhaustively washed with 2 N acetic acid. The ultraviolet absorption spectra of this solution showed a close resemblance to a solution of authentic 2-pyridylacetic acid which was processed through the resins by the procedure that was used for the experimental urine. Comparison of the spectral data with that from known quantities of 2-pyridylacetate in the region 263–264 nm, led to a calculation that the processed urine at this point contained 6.9 moles of 2-pyridylacetate, or 94 6 % of the Serc that has been administered to the animals. The solution was examined by thin-layer chromatography on silica gel, using methanol chloroform (15 85) as the solvent. A single Koenig positive zone at R 0 12 corresponded in R value to that of authentic 2-pyridylacetate.[1]

Additional confirmation of the presence of 2-pyridylacetate was achieved by converting the residual acids to methyl esters by treatment with methanol-sulfuric acid (Konzett, Bost Bowman, Bowman & McKennis, 1971) The methyl ester fraction was treated with picric acid to obtain the picric acid salt of methyl 2-pyridylacetate, m p 143–145 (undepressed by admixture with authentic material). Analysis. calculated for C ,H_{12}N O_9 [380.3], C 44 2 H 3 18 N 14 73 Found. C 44 1 H 3 09 N 14 58. The product cochromatographed with authentic material in Solvent K (McKennis, Turnbull & Bowman, 1964) and showed an infrared absorption spectra (Fig. 2) in good agreement with authentic material

Although no precise information is available on the enzymes responsible for the metabolic degradation of Serc in mammals, hypothetical routes in the metabolism of the compound (Fig. 3) can be constructed from studies on analagous substances. If monoamine oxid-

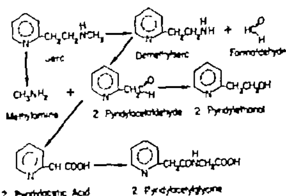


Fig 3 Abridged hypothetical metabolic scheme for metabolic alteration of the side chain of Serc.

ase is the prevailing enzyme in initial oxidation of the side chain, 2-pyridylacetaldehyde and methylamine can be expected as products. An oxidative removal of the N-methyl group of Serc would provide 2-(2-aminoethyl)pyridine and provide formaldehyde which is capable of entering one-carbon pools. Further oxidation of 2-(2-aminoethyl)pyridine would form an alternate route to 2-pyridylacetaldehyde. Oxidation of this aldehyde would provide 2-pyridylacetate. Conversely a reduction of 2 pyridylacetaldehyde would yield 2-pyridylethanol. There is already evidence (Burns, Duncan & Scales, 1967) that 2-pyridylethanol can be metabolized to 2-pyridylacetate From the information then available consideration was given to the possibility that all of the compounds shown in Fig. 3 might play a part in controlling or terminating the characteristic effects of Serc on the microcirculation.

Effect of Serc on vascular resistance

Prior to our studies on the effects of Serc and related compounds in vascular resistance, [illegible] son & Barnes (1972) [illegible] a series of investigations pointing to beneficial effects of Serc in treating certain peripheral vascular diseases in man. Segal ([illegible]) has provided data showing increases in cerebral circulation following administration of Serc [illegible] Sup & Snow (1949) [illegible] that Serc brought about increased cochlear blood flow in the guinea pig. Anderson & Kubicek ([illegible]) [illegible]

[illegible]

Dr H Holmsen-Christensen (private communication) has kindly informed us of chromatographic evidence for the metabolism of Serc to 2 (2-aminoethyl)pyridine and pyridylacetate in man.

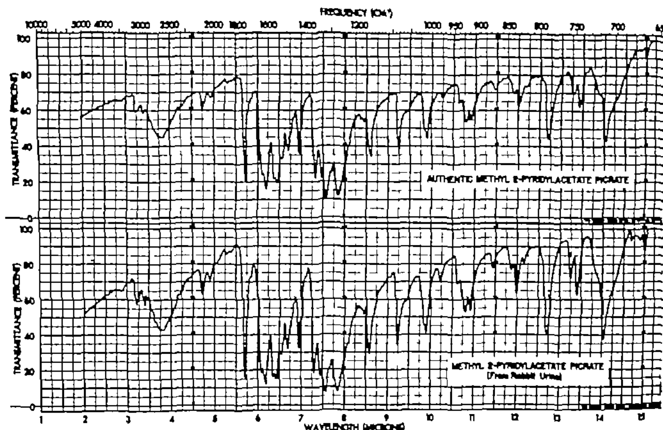


Fig 2 Comparison (in KBr pellet) of the infrared spectra of authentic methyl 2 pyridylacetate picrate and specimen prepared from 2 pyridylacetate from the metabolism of Serc.

during the subsequent 48-hour period. The method for preliminary analysis of the urine is relatively simple and depends essentially upon a separation of metabolites into groups, depending upon their acidic, basic, or neutral behavior

In a typical experiment with rabbits, the urine from 6 animals (approx 2 kg each) was pooled After clarification with diatomaceous earth the urine was passed onto a column of Dowex 50 H which retains or retards acidic and basic metabolites of Serc in which the pyridine ring is intact The column effluent and water washes did not give a positive Koenig test for pyridine compounds and were discarded The column was then eluted with 5 N ammonium hydroxide, which displaced both amphoteric and basic components, including any unchanged Serc, which might be present. Previous studies with other pyridine compounds have indicated (McKennis, Turnbull & Bowman 1963) that many quaternary ammonium compounds formed by the biological N methylation of the pyridine ring can be removed from the column for later investigation by washing the column well with hydrochloric acid.

A preliminary investigation of the ammoniacal eluate based upon UV absorption at 263 nm suggested that approximately 95% of the administered Serc was present in this fraction in some form or other This result was indicative of rather effective elimination of the drug by urinary excretion and led us to examine the urine further The ammoniacal solution was then placed upon a column of Dowex 21 K (OH) The effluent and water wash from this column on the basis of ultraviolet absorption and thin layer chromatography contained at the most only trace quantities of basic pyridine compounds which would include unchanged Serc, and possible basic metabolites, such as 2 pyridylethanol 2-(2-aminoethyl)pyridine and 2 pyridylacetal

and comparison of infrared spectra with an authentic sample.

Although the ultraviolet absorption assay of the acidic fraction of processed urine can be used as an indicator for the presence of acidic metabolites of Serc along with other procedures, some caution must be used in interpretation. In studies on the metabolism of 2-(2 methoxyethyl)-pyridine which is metabolized via the intermediate 2-pyridylethanol to 2-pyridylacetate Burns et al. (1967) have considered the possible presence of 2-pyridylacetylglycine as a metabolite This compound in addition to possible other acidic metabolites such as a glucuronide and a sulfuric acid ester of 2-pyridylethanol would be expected, if present, to show ultraviolet absorption similar to that of 2-pyridylacetate and thus enhance the value calculated for 2-pyridylacetate.

Factors controlling the metabolism of Serc to 2-pyridylacetate

The demonstration that 2-pyridylacetate is a metabolite of Serc in the dog and the rabbit has focussed attention on the source of the enzymatic mechanism responsible for this conversion. Serc was incubated (Bowman et al., 1970 *b*) aerobically with a 12 000 *g* supernatant fraction from homogenized rabbit liver that had been fortified by addition of TPNH. By application of thin-layer chromatography and ion-exchange resins, five Koenig-positive components were separated from the incubation mixture. The ultraviolet absorption of the acidic fraction from the incubation of 1.5 μmoles of Serc with fortified homogenate at 37 for 2 hours indicated the formation of 0.11 μmoles of 2-pyridylacetate, or material with similar ultraviolet absorption characteristics

In addition to further consideration of the metabolism and elimination of Serc from man and other animals, it will be of interest to extend studies that already show a negative effect of antihistaminics on the metabolism and pharmacological effects of Serc. Werle & Palm (1953) have noted the inhibitory effect of anta-

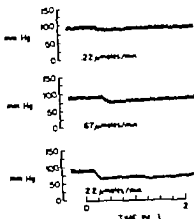


Fig 5 Effect of -(2-aminoethyl)pyridine on the ulnar artery blood pressure of the surgically prepared forelimb of th. dog with blood t constant rate of flow

zoline on the ability of Serc to contract isolated strips of gut. Konzett & Bost (1970), as part of studies on the effect of Serc on peripheral vascular resistance, noted that pretreatment with chlorpheniramine served to reduce the effects of both histamine and Serc on the perfusion pressure.

The use of antihistaminics concurrent with the use of Serc in human medicine although it has occurred, has not been thoroughly studied. The available information on constrictor effects of antihistaminic compounds on the microcirculation (Schayer 1963) implies that these substances under some conditions may make it more difficult for Serc to do its job effectively

ACKNOWLEDGEMENTS

Appreciation is expressed to the U.S. National Institutes of Health (NIH grant no 1 RO1 NS00966) for support of these studies, to the Research Department of UNIMED Inc Morristown, N.J for samples of Serc, and to the Clinical Research Department of N V Philips-Duphar Weesp The Netherlands, sponsors of the Symposium on Ménière Syndrome. Mr R. W Phillips of the Department of Research and Development, the American Tobacco Company kindly determined the infrared spectra. Participation of Professor Konzett in some of the studies was made possible by a National Science Foundation Fellowship.

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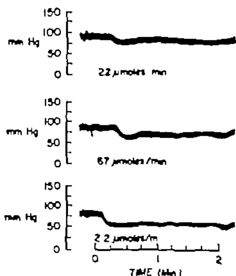


Fig 4 Effect of Serc on the ulnar artery blood pressure (*ordinate*) of the surgically prepared forelimb of the dog with blood at constant rate of flow

Serc increased blood flow through the basilar artery in the dog The experimental procedure developed by Haddy (1960) for studying peripheral vascular resistance in the forelimb of the dog was modified for our purposes and is relatively simple

With the animals under pentobarbital anesthesia and artificial respiration extracorporeal circulation was established (Konzett et al. 1971) by pumping blood at constant flow rate and 37 to the cannulated brachial artery of the right forelimb After proper tie-offs were established, pressures in the ulnar artery close and proximal to the carpus and in the accessory cephalic vein were recorded by means of a polygraph and transducers. At the beginning of the experimental period the flow of the heparinized blood was adjusted at the pump to give a nominally normal perfusion pressure at the ulnar artery Test substances were introduced into the system at a point close to cannula in the brachial artery in 0 9% sodium chloride (0 46 ml/min) Changes in ulnar artery pressure were used as a measure of vascular resistance change. When responses from Serc (Fig 4) and 2-(2-aminoethyl) pyridine (Fig 5) were compared at a dosage of 0 22 to 2.2 μmol/min for 2 min the responses (per cent change in ulnar artery pressure measured at the lowest point within 2 min after injection of the test substance) were not significantly different at the 95% confidence level ($N=5$). Under these conditions, histamine is approximately 200 times more active than Serc base, 2.2 μmoles of Serc base gave a mean percentage fall in ulnar artery pressure approximately equal to that from 0 011 μmoles of histamine base. While the recovery of preinjection pressures was almost immediate or within 1 min, after cessation of the infusion of Serc, return to preinjection pressure after administration of histamine was slower and at some of the higher dose levels (0 11–0 22 μmol/min) required as much as 10 min Pressures at the accessory cephalic vein and the carotid artery were unchanged by administration of the test substances.

2(2 hydroxyethyl)pyridine a putative metabolite of Serc, was administered at dose levels up to 22 μmol/min There were no significant changes in pressure at the ulnar artery acces sory cephalic vein or carotid artery 2-pyridylacetic acid which had already been established as a metabolite of Serc in the rabbit was administered without effect on the measured pressures at doses up to 22 μmol/min

Isolation of 2 pyridylacetate as a urinary metabolite of Serc in the dog

Two male mongrel dogs were give 15 mg of Serc in aqueous solution daily by stomach tube during a period of 8 days. The urine which was initially collected over sodium fluoride, was frozen daily for subsequent processing The combined urines were processed by essentially the same procedures that have been described for the experiments on rabbits. From ultra violet absorption of the solution obtained by treating the Dowex 21 K (OH) column with acetic acid it was calculated that 1.58 g, or 45 1 of the administered Serc had been excreted as an acidic metabolite Confirmation of the presence of 2-pyridylacetic acid was achieved by esterification with methanol-sulfuric acid. The resultant methyl 2-pyridylacetate was converted to a picric acid salt and identified by melting point, mixed melting point

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D M. Martinez

From th Neurotology Research Laboratory Department of Otolaryngology South estern Medical School (Uni ersity of Texas) at Dallas, Texas, USA

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The effect of anaphylactic shock upon these vessels was also previously reported from our laboratory (Weille, Martinez, Gargano Irwin, Gilchrist & Gordon, 1954). The changes noted in the blood vessels of the spiral ligament during anaphylaxis included constriction of the arterioles and initial constriction followed by a dilatation of the venules of the spiral ligament and stria vascularis. Emboli and thrombi were observed in both arterioles and venules.

In a later report (Martinez, 1965) it was demonstrated that anaphylactic shock can produce endolymphatic hydrops in experimental animals (Fig. 2). The dilatation of the scala media was similar to that seen in histological sections of temporal bones of patients who had had Ménière s disease.

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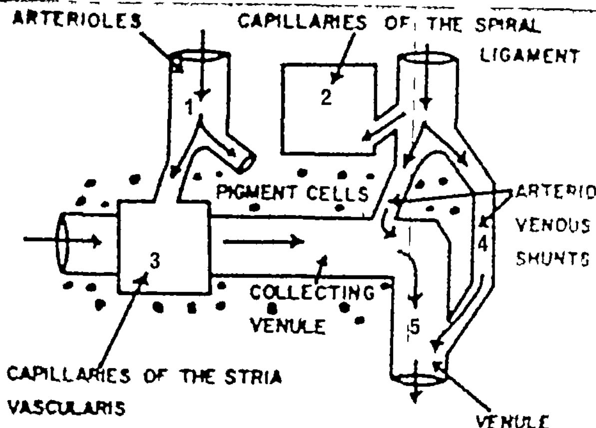


Fig 1 Diagram of the capillary circulation of stria vascularis in the guinea pig *1* arterial *2* network of the spiral ligament *3* network of the stria vascularis *4* arterial venous anastomosis, *5* collecting venule

evidence supports the fact that the endolymph is produced, for the most part, by this structure Allergic reactions or other factors affecting the capillary vessels of the stria vascularis producing a sustained vessel constriction has been considered as a cause for increasing the pressure in the endolymph (Fig 3)

This series of experiments was undertaken to determine the possible changes occurring in the capillaries of the stria vascularis and spiral ligament under the effect of betahistine hydrochloride

METHOD

Over 150 experiments were performed utilizing guinea pigs and chinchillas (Fig 4) The weights varied from 00 to 600 g for the guinea pigs and from 400 to 600 g for the chinchillas. These experimental animals were chosen because of their relative small size and because their cochleas could be made surgically accessible for this type of experiment. The technic has been reported in the previous publications quoted

Each animal was anesthetized by the interperitoneal injection of sodium phenobarbital 45 ml/kg of body weight Additional doses were administered as required during the course of the experiment.

The operative procedure consisted of five stages (1) tracheotomy (2) macroscopic exposure of the cochlea, (3) microscopic fenestration of the second or third turn of the cochlea over the scala media (4) observations of normal circulation and (5) application of betahistine hydrochloride topically intravenously and intragastrically through a plastic feeding tube Each of these steps is discussed in detail.

Tracheotomy

Oxygen was administered via endotracheal tube throughout the experiment Frequent PO_2 and PCO_2 determinations were made to ensure that normal levels were maintained

Macroscopic exposure of the cochlea

The cochlea was exposed by post-auricular incision and partial removal of the mastoid bulla (Fig. 5)

Microscopic dissection

The exposure of spiral ligament and the stria vascularis were made with a microdrill suported by a micro-

Fig. 2 Temporal bone cross-section showing dilatation of the scala media of the guinea pig with artificially induced hydrops by an anaphylactic shock.

manipulator (Fig. 6) The preparation was kept at a constant temperature by means of mammalian Ringer solution at 38°C flowing gently on the cochlea. Light to visualize the cochlea was provided by a 1 000 W projection bulb and transmitted via fiber-optic rod. In order to avoid trauma, exposure of the spiral ligament was made by means of polishing burr The operator circumscribed an area of bone measuring 1 mm in the horizontal plane and 0.5 mm in the vertical plane of the cochlear base. The bone was thinned down to its endosteum The circumscribed area plus the underlying endosteum were then raised gently and removed with microsurgical pick. Bone chips were thus avoided and clean sharp edges of

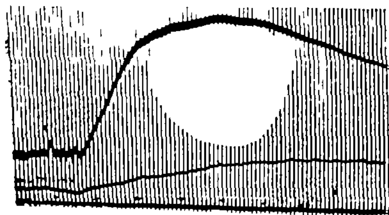


Fig. 3 Graphic showing pressure changes of the endolymph and arterial pressures of the guinea pig under anaphylaxis

Fig 4 Experiment in progress for the study of the capillary circulation of the stria vascularis with the use of betahistine hydrochloride.

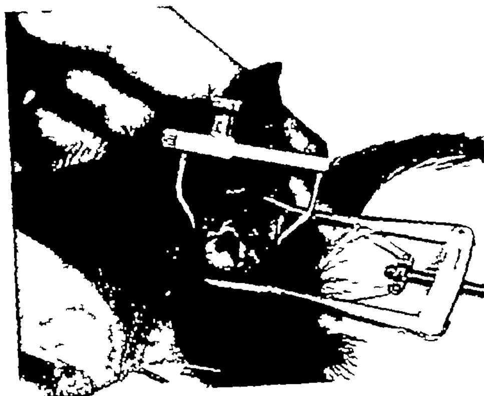


Fig 5 Cochlea expose

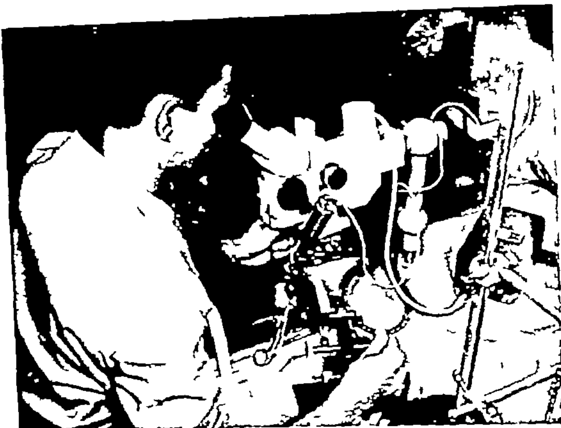


Fig 6 Fenestration of the cochlea

the fenestra were obtained Observations were made with 15 ocular and 11 ultrapack objective During the course of the microscopic exposure of the cochlea, the stapes was left undisturbed.

The location of the stria vascularis was made by determining an area limited by the two bone portions that separate cochlear turn where the pigment of the stria vascularis shows in dark animals With added experience, albino animals were utilized in order to avoid the pigment in the stria vascularis that interferes with the visualization of the capillary vessels of the stria vascularis

The jugular veins were then exposed A cannula containing mammalian Ringer solution and heparin was placed in each jugular vein One of the cannulas was connected to monitoring equipment for venous pressure measurements, the other cannula was utilized to inject betahistine hydrochloride or other drugs when the intravenous route was explored In other experiments, the common carotid artery was cannulated for monitoring the arterial pressure

I another group of experiments, plastic catheter as inserted through the esophagus into the stomach of the animal The animal was placed on a special table constructed according to the method of Peck & Hoerr (1951) for the purpose of minimizing vibrations

Table I

Albino guinea pig, 350 g
0 26 ml Nembutal p
Tracheotomy performed
Cochlea exposed right ear fenestration performed
0 1 mg topical Serc applied in 0 1 ml mammalian Ringer solution

Time (post-application)	Observations
5 s	Immediate dilatation of arterioles, venules, and capillaries
30 s	Continued dilatation, blood flow essentially the same
1 m	Continued dilatation
4 m	Decreased dilatation, blood flow the same or decreased
10 m	Irrigation with Ringer lactate
20 m	Blood vessels to initial diameter

Topical application of betahistine hydrochloride produced immediate dilatation of short duration at this concentration with no marked change in blood flow

Fig 4 Experiment in progress for the study of the capillary circulation of the stria vascularis with the use of betahistine hydrochloride

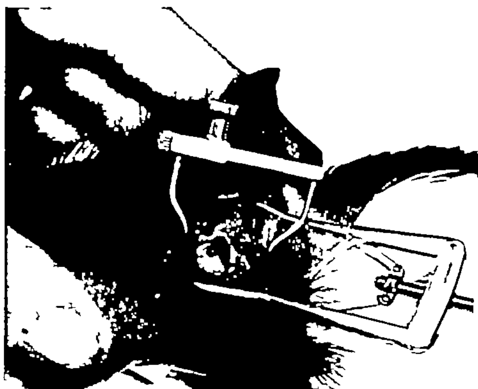


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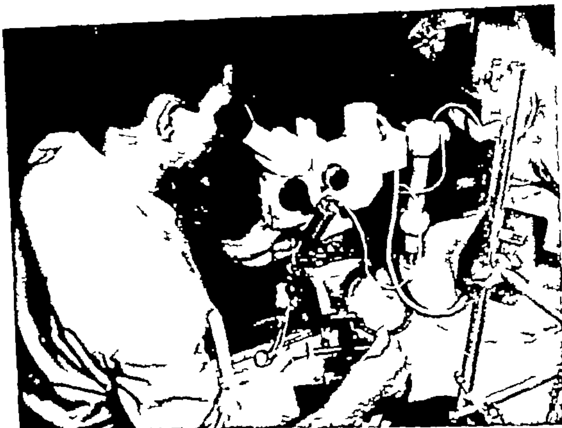


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Tracheotomy performed
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Time (post-application)	Observations
3 s	Immediate dilatation of arterioles, venules, and capillaries
30 s	Continued dilatation, blood flow essentially the same
1 m	Continued dilatation
4 m	Decreased dilatation, blood flow the same or decreased
10 m	Irrigation with Ringer lactate
20 m	Blood vessels to initial diameter

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Table II

Albino guinea pig, 376.1 g
0.26 ml Nembutal I p.
Tracheotomy performed
Cochlea exposed right ear fenestration performed
Left external jugular cannulated
0.1 mg (0.1 ml) Serc IV injected

Time (post injection)	Observations
45 s	Dilatation of both venules and arterioles Speed of blood flow increased Good dilatation of venules and arterioles Temp 37.8°C
2 m	*Temp 36.6°C*
2 m 30 s	Arterioles and venules still dilated
3 m	Animal alive and breathing well
3 m 20 s	*Dilatation begins to decrease*
3 m 45 s	Blood flow still increased
4 m	Arterioles show less dilation than before
4 m 30 s	Dilatation of arterioles to pre injection, level
4 m 50 s	Dilatation of venules to pre-injection, level
5 m	Blood flow returned to normal rate

Dilatation of arterioles, venules, and capillaries noted with *this concentration of betahistine hydrochloride. The blood* flow also increased These changes were of very short dura tion.

OBSERVATIONS

The initial venous and arterial pressures were recorded and the exposed blood vessels studied. The vessels studied included. arterioles, arteriovenous anastomosis, capillaries, and venules of the spiral ligament as well as the capillary network of the stria vascularis. The blood vessel had to meet *the following quali* fications to be considered in arteriole of the spiral *ligament*. It had to be located in the spiral ligament and had to take the shape of a cone with a direction of linear flow going from the larger end of the cone toward the smaller In general no part of any arteriole had a diameter greater than 60 μ Capillaries were of smaller diameter

The capillaries appeared in the spiral liga ment as an intricate network of dividing and anastomosing tubules receiving flow from ar terioles. The arteriovenous anastomoses were vessels of the spiral ligament. They started off as branches of the arterial and entered directly into a venule without intervening capillary net work At no point did such an anastomosis look like a cylinder The *capillaries of the* stria vascularis were found in the area of pigment cells. These capillaries form a net work of branching and anastomosis cylinders and they too emptied into the venules of the spiral ligament These venules took the form of cones with a direction of linear flow from the part of the vessel with the smaller diameter towards that with the larger diameter Some of these venules ran horizontal to the field, and these in turn ran into venules that were *perpendicular to the field.*

Application of betahistine hydrochloride

Topical application of a solution of betahistine hydrochloride (2 mg in 10 ml of mammalian Ringer solution) produced an immediate dilatation of the arterioles, an increase of ar teriolar blood flow dilatation of the venules, although in lesser degree than that of the ar terioles. An increase in capillaries was noted on visual examination (Table I)

The intravenous administration of beta histine hydrochloride was made in several con centrations, the lowest being 0 1 mg in 0 1 ml of Ringer solution As seen in Table II, dilata tion of the arterioles and venules with in creased blood flow in the spiral ligament and stria vascularis were noted as early as 45 sec after injection These changes lasted in this *experiment until 5 min post-injection Larger* doses of betahistine hydrochloride injected in travenously increased the periods of vasodila tation and of increased blood flow The prolonged vasodilatation reached an optimum with the larger doses, after which it appeared to remain the same without further increase (Tables III IV V)

The effect on the capillary circulation should not be examined alone but should be con sidered together with other possible changes in venous and arterial pressures. A number of experiments were done in order to demon strate the effect of betahistine hydrochloride on the venous and arterial pressures of ex perimental animals.

ble III

bino guinea pig, 365 6 g
ml Nembutal injected p.
acheotomy performed
chlea exposed right ear
ft external jugular vein cannulated
nestra made in cochlea

jection	Time (post-injection)	Observations
2 mg (0 1 ml) Serc IV	1 m	Vasodilation of arterioles with increased speed of blood flow
	1 m 10 s	Vasodilation of venules
	3 m	Still dilated, slow down in flow of venules
	3 m 25	Vasodilation still present
	3 m 45 s	Capillaries appearing
	4 m 35 s	Vasodilation maintained
	5 m 15 s	Blood flow still increased
	6 m 30 s	Venules back to original size
	6 m 55 s	Arterioles still dilated
	8 m 20 s	One arteriovenous arcade in field which follow changes of arterioles described above
	9 m	Decreasing dilation of arterioles but still above initial size
	9 m 40 s	Smaller arterioles to stria vascularis back to original level
	10 m 50 s	Blood flow still increased in arterioles
	14 m 50 s	Arterioles decreased in size but still slightly above initial level
	15 m 20	Blood flow still bove initial level
	21 m	Temperature 37 1°C
	23 m	Arterioles back to initial size
0 3 mg (0.1 ml) Serc IV	1 m 20 s	Vasoconstriction of arterioles
	1 m 40	Arterioles to original size
	3 m	Increased flow in arterioles and venules and beginning dilation of arterioles
	3 m 15	Further dilation of venules
	3 m 40	Arterioles have increased 50 % in size
	4 m 35	Flow still increased in arterioles and venules
	7 m 50	Temperature 37 7°C
	9 m 40	Blood flow and arterioles back to initial level
0 5 mg (0 1 ml) Serc IV	45	Vasoconstriction of arterioles
	1 m 20	Blood flow in venules slowed
	1 m 35	Arterioles dilating
	2 m 10	Blood flow increasing
	2 m 50	Further dilation of arterioles, venules essentially unchanged
	7 m 25	Arterioles to initial level
	7 m 50	Circulation in arterioles still increased
	8 m 5	Circulation in venules to initial level

The first administration of betahistine hydrochloride in this experiment produced definite vasodilatation and increased blood flow as early as 1 min after injection Further additions of betahistine produced an initial vasoconstriction of arterioles followed by dilatation but did not increase markedly the duration of this effect The vasodilator effect was of about 50 % of the initial diameter of the blood vessels.

These experiments were done injecting as little as 0 2 mg of betahistine hydrochloride intravenously (Table VI) The changes of venous and arterial blood pressures were minimal. Slight changes were more evident when the dose was increased to 0 3 mg IV (Table VII) In this case, a slight increase in arterial pressure was present within 2 min following injection, after which it returned to its original level and decreased slightly for a period of about an hour Changes were considered significant when they were more than 0.5 mmHg for venous pressure and 5 mmHg for arterial pressure in either direction. The variations in pressure appeared to be related to the concentration of the solution injected. The volume of the solvent was kept equal in all concentrations (Tables IX, X XI).

Table IV

Albino guinea pig, 367.5 g
0.30 ml Nembutal injected i p.
Tracheotomy performed
Left external jugular cannulated
Cochlea exposed right ear fenestration performed
1.0 mg (0 1 ml) Serc IV injected

Time (post injection)	Observation
10 s	Vasoconstriction of arterioles and venules
25 s	Vasodilatation, marked increased blood flow
1 m 15 s	Marked dilatation, neo arterioles and neo venules
2 m 20 s	Venules dilated two-fold
[illegible] m 30 s	Capillaries dilated, arterioles also dilated two-fold
5 m 45 s	Dilatation still present in all vessels
6 m 10 s	Blood flow increased
7 m 45 s	Vasodilatation persists, increased blood flow persists
8 m 25 s	Vasodilatation still persists, increased blood flow persists
11 m 30 s	Vasodilatation persists, blood flow slowing down
15 m 50 s	Dilatation still present, blood flow slightly above normal in arterioles
16 m 40 s	Blood flow to normal in venules
22 m	Vasodilatation remains

Larger dosage (1 mg) of betahistine hydrochloride showed a very transitory vasoconstriction followed by marked vasodilatation, the latter lasting for over an hour

Table V

Chinchilla 360 g
0 40 ml Nembutal injected i.p.
Tracheotomy performed
Right external jugular cannulated
Cochlea exposed right ear fenestration performed
4 0 mg (0.1 ml) Serc IV injected

Time (post injection)	Observations
5 s	Tachypnea
39 s	Marked vasodilation of arterioles
1 m 35 s	Increased blood flow
2 m 40 s	Dilatation of capillaries, more are visible
2 m 58 s	Venules dilated
4 m 15 s	Many capillaries visible
6 m 55 s	Less noticeable dilation of venules, arterioles still dilated about two-fold
16 m 45 s	Arterioles still dilated, blood flow increased still, venules still dilated, capillaries still dilated
23 m	Arterioles [illegible]0 μ in diameter
27 m 40 s	Blood flow still increased
28 m 30 s	Arterioles still 20 μ
29 m 15 s	Capillaries appear less red, possibly larger amount of plasma than initially
29 m 30 s	Arterioles [illegible]5 μ
35 m 40 s	Capillaries are dilated, arterioles still dilated to [illegible]5 μ blood flow still increased
47 m 40 s	Capillaries still dilated, arterioles still dilated, blood flow still increased

The larger dosage of betahistine hydrochloride (4 0 mg) administered to the chinchilla produced tachypnea and marked vasodilatation and increased blood flow which lasted more than 1 h.

Table VI

Brown and white guinea pig, 451.2 g
0 36 ml Nembutal injected i p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection arterial pressure recorded at 45 mmHg
0 2 mg Serc (0 1 ml) IV injected

Time (post-injection)	Arterial pressure (mmHg)
1 m	42
2 m	51
3 m	52
4 m	52
5 m	51 3
6 m	51 5
7 m	51
8 m	50 6
9 m	50
10 m	49 3
11 m	49
12 m	42.5
13 m	41
14 m	40 6
15 m	42.3
16 m	43
17 m	43
18 m	43 5
19 m	41 3
20 m	44
21 m	44 6
22 m	44
23 m	44
24 m	44
25 m	43 6
30 m	45
35 m	44
40 m	43 5
45 m	43

Administration of 0 2 mg betahistine hydrochloride IV showed no significant change in arterial pressure.

Table VII

Albino guinea pig, 319 3 g
Injected 0 25 ml Nembutal i.p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection arterial pressure recorded at 49 mmHg
0.3 mg (0 1 ml) Serc IV injected

Time (post-injection)	Arterial pressure (mmHg)
1 m	68
2 m	78
3 m	76
4 m	48 5
4 m 15	42
5 m	48
6 m	46
7 m	43
8 m	44
9 m	43
10 m	42
11 m	42
12 m	40
13 m	39
14 m	38
15 m	37
16 m	38
17 m	43
18 m	44
19 m	44
20 m	42
21 m	46
22 m	50
23 m	45
24 m	44
25 m	45
55 m	40

0 3 mg betahistine hydrochloride produced a slight initial increase in arterial pressure followed by more prolonged decrease.

Table VIII

Brown and white guinea pig, 346.9 g
0.?7 ml Nembutal injected i p
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection arterial pressure recorded at 39 mmHg
0.1 ml Ringers injected IV

Time (post injection)	Arterial pressure (mmHg)
1 m	39.5
? m	37
3 m	38
4 m	38
5 m	36.5
6 m	36.5
7 m	33.5
8 m	33
9 m	33
10 m	3
11 m	35
1 m	40
13 m	41.5
14 m	4
15 m	40.5
16 m	36
17 m	40
18 m	38
19 m	39
?0 m	40
25 m	40
30 m	38 6
35 m	40.5
40 m	39
45 m	39.5
50 m	38
55 m	36.5
60 m	37

Control experiment to demonstrate the lack of arterial pressure changes in the guinea pig when 0.1 ml of Ringer lactate is injected intravenously

Table IX

Chinchilla, 418 4 g
0.50 ml Nembutal injected I p
Tracheotomy performed
Left external jugular vein cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre injection pressure recorded venous, 1.86, arterial, 53 (mmHg)
4 0 mg (0.1 ml) Serc injected

Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
30 s	1.34	88
1 m	1.34	9
? m	1.50	80
3 m	2.00	60
4 m	1.00	5
5 m	0.86	49
6 m	0 67	45
7 m	0 86	40
8 m	1 17	37
9 m	1.34	48
10 m	1 67	52
11 m	1 86	55
15 m	1 67	59
20 m	1 67	59
?5 m	1.50	60
30 m	1 67	7?
35 m	1.86	64
40 m	1 66	68
45 m	1 67	68
50 m	1 67	72
55 m	1.50	76
60 m	1 67	80
65 m	1 67	80
70 m	1 86	76
75 m	1 86	68

4 0 mg betahistine hydrochloride produced an initial decrease in venous pressure lasting 65 min. The arterial pressure, after initial increase, had a decrease of short duration.

Table X

Chinchilla, 366 3 g
Injected 0 40 ml Nembutal I p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded, venous, 1 86, arterial, 54 (mmHg)
4 0 mg (0 1 ml) Serc IV injected

Time (post-injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
15 s	1 17	41
30	1 34	37
1 m	1 50	40
2 m	1 86	44
3 m	00	46
4 m	2 00	46
5 m	2 34	46
6 m	2 17	45
7 m	1 86	47
8 m	2 00	43
9 m	2 17	49
10 m	2 17	54
15 m	—	55
20 m	2 50	57
30 m	2 50	56
35 m	2 67	59
40 m	2 86	57
45 m	3 00	56
50 m	2 50	57
55 m	2 50	60
60 m	2 67	59

4 0 mg betahistine hydrochloride produced slight decrease of venous pressure followed by slight increase There was more definite decrease in the arterial pressure

Table XI

Chinchilla, 390 6 g
0 46 ml Nembutal injected p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded enous, 1.17 arterial, 75 (mmHg)
4 0 mg (0 1 ml) Serc IV injected

Time (post-injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
30 s	1,50	84
1 m	1 17	72
m	1 00	64
3 m	1 17	62
4 m	1,36	60
5 m	1 36	60
6 m	1 17	60
7 m	1 17	60
8 m	1 17	64
9 m	1 17	64
10 m	1 17	64
15 m	1 00	68
20 m	1 17	68
25 m	1 00	72
30 m	1 17	64
35 m	1 17	76
40 m	1 00	76
45 m	0 86	76

4 0 mg betahistine hydrochloride IV enous pressure essentially unchanged. Arterial pressure moderately decreased

Table XII

Chinchilla, 529.2 g
0.63 ml Nembutal injected i.p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 0.50 arterial 80 (mmHg)

Injection	Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
0.1 ml Ringers IV	1 m	0.37	80
	2 m	0.50	84
	3 m	0.50	80
	4 m	0.67	80
	5 m	0.50	80
	6 m	0.67	84
	7 m	—	—
	8 m	0.86	84
	9 m	0.86	86
	10 m	0.86	84
	15 m	0.67	76
	20 m	0.86	80
0.2 mg (0.2 ml) Histamine IV	1 m	1.00	86
	2 m	0.67	54
	3 m	0.67	44
	4 m	0.86	36
	5 m	0.50	30
	6 m	0.50	21
	7 m	0.17	4
	8 m	0.50	23
	9 m	0.67	23
	10 m	0.86	29
	15 m	—	40
	20 m	0.86	60
	25 m	0.86	74
	30 m	0.86	80
	35 m	0.67	80
	40 m	0.67	84

0.1 ml of mammalian Ringer solution IV produced venous pressure and arterial pressure changes within the allowed range considered not significant under the conditions of this experiment (0.5 mmHg for venous pressure and 5 mmHg for arterial pressure in either direction) 0 mg of histamine produced essentially no change in venous pressure and a moderate decrease of short duration in the arterial pressure.

Table XIII

Chinchilla, 436.6 g
0.52 ml Nembutal injected i.p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 1.36 arterial, 68 (mmHg)
0.25 mg (0.25 ml) Histamine IV injected

Time (post-injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
15 s	0.50	80
1 m	0.50	64
2 m	0.67	57
3 m	0.67	49
4 m	0.86	41
5 m	0.36	36
6 m	0.50	32
7 m	0.50	32
8 m	0.50	32
9 m	0.50	3
10 m	0.50	32
15 m	0.67	36
20 m	—	44
25 m	0.67	46
30 m	1.00	57
35 m	1.17	62
40 m	0.86	59
45 m	—	58

0.25 mg histamine IV produced a definite decrease of venous and arterial pressure.

Table XIV

Chinchilla, 465.3 g
0.56 ml Nembutal injected i.p.
Tracheotomy performed, cochlea exposed, fenestration performed
Left external jugular cannulated
Right common carotid cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection pressure recorded: venous, 1.84; arterial, 84 (mmHg)
4.0 mg (0.4 ml) Serc injected via esophageal tube

Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)	Observations
1 m	2.17	80	
2 m	2.17	84	
3 m	2.00	84	
4 m	1.84	88	
5 m	2.00	84	
6 m	1.67	92	
7 m	2.00	88	
8 m	2.17	88	
9 m	1.84	88	Arterioles dilated, blood flow increased, venules also dilated
10 m	1.84	88	
15 m	1.67	88	Capillaries visible, dilatation of arterioles and venules still present
20 m	1.84	80	
25 m	2.17	84	
30 m	1.84	86	
35 m	1.84	76	
40 m	2.00	72	
42 m	1.34	64	Venules still dilated, capillaries still visible, arterioles less dilated, blood flow still increased
45 m	1.84	80	
50 m	1.84	80	Venules dilated, arterioles to original size, capillaries not visible, blood flow still increased

4.0 mg betahistine hydrochloride administered intragastrically via esophageal tube showed venous pressure essentially unchanged. Arterial pressure showed a slight increase followed by a slight decrease. Vasodilatation occurred as the blood pressure decreased.

Table XII

Chinchilla, 529.2 g
0 63 ml Nembutal injected i p
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 0.50 arterial, 80 (mmHg)

Injection	Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
0 1 ml Ringers IV	1 m	0 37	80
	2 m	0.50	84
	3 m	0.50	80
	4 m	0 67	80
	5 m	0.50	80
	6 m	0 67	84
	7 m	—	—
	8 m	0 86	84
	9 m	0 86	86
	10 m	0 86	84
	15 m	0 67	76
	20 m	0.86	80
0.2 mg (0.2 ml) Histamine IV	1 m	1.00	86
	2 m	0 67	54
	3 m	0 67	44
	4 m	0 86	36
	5 m	0.50	30
	6 m	0.50	1
	7 m	0 17	24
	8 m	0 50	23
	9 m	0 67	23
	10 m	0 86	29
	15 m	—	40
	20 m	0 86	60
	25 m	0 86	74
	30 m	0 86	80
	35 m	0 67	80
	40 m	0 67	84

0 1 ml of mammalian Ringer solution IV produced venous pressure and arterial pressure changes within the allowed range considered not significant under the conditions of this experiment (0.5 mmHg for venous pressure and 5 mmHg for arterial pressure in either direction) 0 2 mg of histamine produced essentially no change in venous pressure and a moderate decrease of short duration in the arterial pressure

Table XIII

Chinchilla, 436 6 g
0.52 ml Nembutal injected i.p
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 1.36 arterial, 68 (mmHg)
0 25 mg (0.25 ml) Histamine IV injected

Time (post-injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
15 s	0 50	80
1 m	0.50	64
2 m	0 67	57
3 m	0 67	49
4 m	0.86	41
5 m	0.36	36
6 m	0.50	32
7 m	0.50	32
8 m	0.50	32
9 m	0.50	32
10 m	0.50	32
15 m	0 67	36
20 m	—	44
25 m	0 67	46
30 m	1 00	57
35 m	1 17	62
40 m	0.86	59
45 m	—	58

0.25 mg histamine IV produced a definite decrease of venous and arterial pressure.

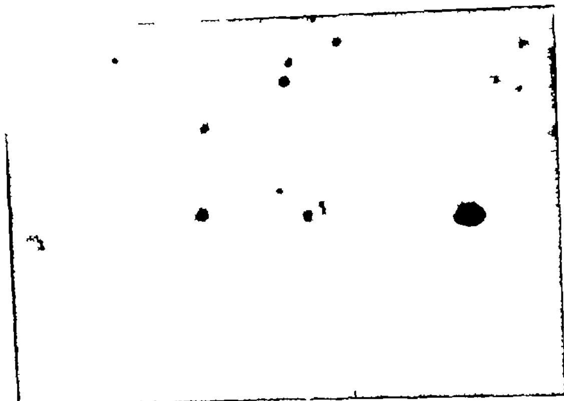


Fig. 8 Circulation of the stria vascularis after administration of intragastric betahistine hydrochloride

SUMMARY OF RESULTS

The observation of the capillary bed of the stria vascularis after intravenous injection of betahistine hydrochloride showed changes with as little as 0.1 mg of the drug. With increased doses, *the changes were more marked to an* optimum level and were of longer duration. The changes seen were those of vasodilatation of the arterioles of precapillary arterioles and increased blood flow within a minute from the injection. This was followed by dilatation of the venules and capillaries. No emboli, blood sludge, or cell aggregates were observed after the injection of betahistine hydrochloride when the preparation was kept free of trauma and the temperature was kept constant. When blood sludge (primarily due to trauma) was seen prior to the administration of the drug, it often disappeared initially with the administration of betahistine hydrochloride.

During the instillation of 4 mg of betahistine hydrochloride via esophageal tube into the stomach changes were noted in the circulation after 8 min from the instillation. These changes consisted of the dilatation of arterioles, *arteriovenous arcades, and increased* blood flow followed by dilatation of venules and capillaries

In the spiral ligament and stria vascularis the increase of capillary size varied three-fold from its original level, that is, from a measurement of 10 μ to a level of 20 to 30 μ during dilatation. The speed of the blood flow in capillaries, arterioles, and venules increased on an average of 50%

The data and results from a selected number of the experiments are shown in Tables I through XIX.

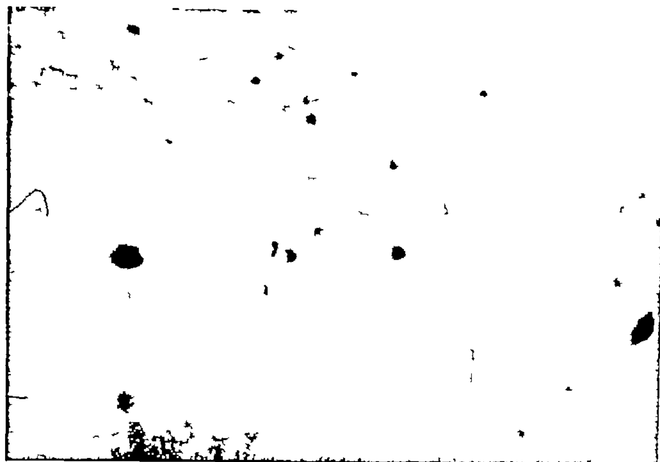


Fig 7 Circulation of the stria vascularis before administration of intragastric betahistine hydrochloride.

Control experiments were done injecting Ringer solution intravenously The changes in arterial and venous pressures were within the 10 mm range (Table VIII) In another group of experiments intravenous histamine was utilized. The changes observed were similar to those seen with betahistine hydrochloride There was an initial increase of pressure during the first minute However the post injection hypotension was more marked and prolonged. The latter was more evident during the 10 min that followed the injection (Tables XII XIII)

Betahistine hydrochloride (4 0 mg) was also administered via esophageal tube into the stomach. The initial slight increase in blood pressure was not noted until after 6 min There was then a decrease in arterial blood pressure (10 mmHg) The hypotension lasted approximately 12 min This occurred 35 min after the *instillation of betahistine hydrochloride via the* esophageal tube The venous pressure changes were negligible (Table XIV and Figs. 7 8)

When 12 mg of betahistine hydrochloride was administered via esophageal tube there was again a minimal initial rise of the blood pressure but the hypotension was more marked appearing 15 min following instillation. The arterial and venous pressures decreased significantly The experimental animals survived this dose (Tables XV XVI XVII XVIII)

In a comparison study the instillation of 0 4 mg of histamine was made into the stomach via esophageal gastric tube Hypotension up to 40 mmHg was noted within 8 min from the instillation of histamine. The venous pressure also decreased but less markedly (Table XIX)

Table XVI

Chinchilla, 506 g
0.60 ml Nembutal injected i.p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection arterial pressure recorded. 56 mmHg
12.0 mg (0.3 ml) Serc injected via esophageal tube

Time (post-injection)	Arterial pressure (mmHg)
1 m	64
2 m	68
3 m	68
4 m	60
5 m	57
6 m	58
7 m	64
8 m	64
9 m	60
10 m	60
13 m	40
15 m	32
16 m	22
17 m	18
18 m	14
19 m	11
20 m	53
25 m	53
29 m	34
30 m	27
33 m	17
34 m	14
35 m	13
36 m	11
40 m	8
42 m	44
45 m	46
50 m	48
55 m	46

12.0 mg of betahistine hydrochloride via esophageal tube produced definite decrease in arterial pressure.

Table XVII

Chinchilla, 487.4 g
0.5 ml Nembutal injected i.p.
Tracheotomy performed
Left jugular cannulated
Left external jugular cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection pressure recorded: venous, 1.87 arterial, 68 (mmHg)
12.0 mg (0.3 ml) Serc injected via esophageal tube

Time (post-injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
1 m	2.00	68
2 m	1.87	64
3 m	—	64
4 m	—	64
5 m	—	64
6 m	2.00	62
7 m	2.17	62
8 m	2.00	64
9 m	2.00	64
10 m	2.50	68
15 m	3.50	80
20 m	3.37	76
25 m	3.17	72
29 m	—	46
30 m	2.67	72
35 m	3.00	72
40 m	3.00	76
45 m	3.00	76
50 m	2.67	76
60 m	2.67	76
65 m	2.67	76

12.0 mg betahistine hydrochloride via esophageal tube produced slight increase in venous pressure with minimal change in arterial pressure.

Table XV

Chinchilla, 454 4 g
0.4 ml Nembutal injected i p
Tracheotomy performed cochlea exposed, fenestration performed
Left external jugular cannulated
Right common carotid cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 2.67 arterial 78 (mmHg)
12.0 mg (0.3 ml) Serc injected via esophageal tube

Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)	Observations
1 m	2.84	76	
2 m	3 00	72	
3 m	2.67	72	
4 m	2.34	68	Arterioles dilated, blood flow increased
5 m	2.34	68	
6 m	2.17	68	
7 m	—	5	Venules dilated, capillaries visible, arterioles still dilated
8 m	1.00	48	
9 m	1.34	62	
10 m	1 67	64	
15 m	1 17	68	Marked dilatation arterioles and venules, blood flow appears decreased
20 m	1 67	7?	
25 m	1 67	64	
30 m	0 67	60	Less dilatation arterioles, venules and capillaries still dilated
35 m	0 87	64	
40 m	0 67	64	
45 m	0 86	60	
50 m	0.86	64	Venules dilated, blood flow decreased

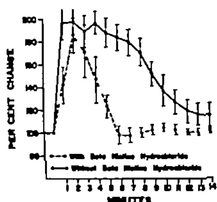


Fig 9 Comparison of venous pressure changes, guinea pig, under an anaphylaxis With betahistine hydrochloride, anaphylactic shock was of shorter duration and the animal survived.

arterioles and arterial venous arcades in stria vascularis and spiral ligament of guinea pigs and chinchillas.

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Table XVIII

Chinchilla, 393.8 g
Injected 0.46 ml Nembutal i p.
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection arterial pressure recorded at 60 mmHg

Time (min)	Post injection arterial pressure (mmHg) 4 0 mg (0 1 ml) Serc injected via esophageal tube	1_0 mg (0.3 ml) Serc injected via esophageal tube[a]
1	55	57
2	57	55
3	54	54
4	56	54
5	53	51
6	54	51
7	55	55
8	54	53
9	50	5
10	49	32
15	56	12
20	54	64
25	52	—
30	37	55
35	36	53
40	62	50
45	51	44
50	45	40
55	58	30

Same animal after pressure returned to pre-injection level. Blood pressure change comparison of 4 0 and 12 0 mg of betahistine hydrochloride given intragastrically and sequentially Slight decrease with first dose and moderate decrease with second dose.

Table XIX

Chinchilla, 4?6.2 g
0.51 ml Nembutal injected
Tracheotomy performed
Left external jugular cannulated
Right common carotid cannulated
Tube placed in stomach via esophagus
Pressure monitoring equipment connected
Pre-injection pressure recorded venous, 3.00; arterial, 80 (mmHg)
0.4 mg histamine (0.4 ml) injected via esophageal tube

Time (post injection)	Venous pressure (mmHg)	Arterial pressure (mmHg)
1 m	2.86	68
_ m	_.17	68
3 m	1 67	64
4 m	2.17	55
5 m	1 84	50
6 m	1 84	48
7 m	1 84	45
8 m	2.67	47
9 m	2.34	41
10 m	2.17	38
15 m	3.34	84
?0 m	3.50	68
2_ m	_50	54
_5 m	3.34	68
30 m	3 34	56
35 m	3 00	40
40 m	1.34	50
45 m	2.50	60
50 m	3.34	88
60 m	3.34	64

0 4 mg histamine administered intragastrically via esophageal tube produced definite initial decrease of venous pressure of short duration. A decrease of longer duration was seen in arterial pressure.

DISCUSSION

In the experiments here described it was observed that betahistine hydrochloride behaves very much like histamine in its effect on the circulation of the spiral ligament and stria vascularis when administered topically and intravenously It was also demonstrated that this effect is present when administered intra gastrically

ADDENDUM

In separate experiments in which an ana phylactic shock was administered to experimental animals, it was noted that those ani mals that were previously given intragastric or intravenous betahistine hydrochloride did not have as severe a shock and survived anaphylaxis when compared to the group not given beta histine hydrochloride where shock was more severe or the animal did not survive (Fig 9)

When the capillary circulation was observed in these experiments, it appeared that the amount of circulating sludge formation and emboli was also decreased

CONCLUSION

In conclusion our experimental studies illustrate that betahistine hydrochloride is capable of producing vasodilatation of capillaries.



g 1 Position of electrodes to record the horizontal ovements of eyes separately technique routinely used. The vertical movement is recorded for one eye only

ng middle or external ear pathology were stimulated by cold air according to Dundas-Grant's technique

TECHNIQUE

(*a*) *Tests for the evaluation of auditory function* The following investigations were done to evaluate the effect of the medication on the auditory function 1) tonal audiometry 2) vocal audiometry 3) Békésy audiometry 4) SISI test 5) recruitment, using Fowler technique when applicable

(*b*) *Test for the evaluation of the vestibular function* Electrodes (Ag Ag Cl) are applied to the internal and external canthi of each eye separately (Fig 1). It must be noted, however that the horizontal nystagmus can also be recorded from both eyes together using the electrodes at both external canthi The purpose of recording each eye separately is to detect dissociated eye movements present in certain pathologies of central origin In order to obtain standardized eye recordings, we always record each eye separately Another electrode is placed above the eye, and coupled with one below the eye, to record the vertical nystagmus (Bertrand & Arbow 1966 Bertrand, 1969)

The maximum allowable impedance between two electrodes is 10 000 ohms The skin is cleaned with ether and a conductive paste is used. Calibration is regulated, so that 20° of angular eye movement produces 16 to 20 mm pen deflection. Recording is done on Schwarzer apparatus, with a paper speed of 1 cm/s, and capacitor coupling with an eight second time constant. On the horizontal plane, an eye movement to the right is recorded as an upward deflection and to the left a downward Likewise, on the vertical plane, an upward movement is recorded upward and vice-versa

Spontaneous and positional nystagmus

Spontaneous nystagmus is studied both with the eyes open and with the eyes closed When studying positional nystagmus, we used the following technique with the following positions: 1 head turned to the right, 2. head turned to the left; 3 on the right side; 4 on the left side 5 ventral 6 head hanging, 7 sitting; 8. supine. W recorded with the eyes closed for at least 30 seconds in each position.

Several criteria can be used for the analysis of spontaneous and positional nystagmus For spontaneous nystagmus, we first recorded its presence or absence with the eyes open and fixed upon small light. We do not, unless there is marked visual asym-

MÉNIÈRE'S DISEASE. SUBJECTIVE AND OBJECTIVE EVALUATION OF MEDICAL TREATMENT WITH BETAHISTINE HCl

R. A Bertrand

From the E.N.T Department Hôpital Notre-Dame Montreal Canada

AIM OF THE STUDY

Histamine is believed to have a certain value in the treatment of Ménière s disease or endolymphatic hydrops. Recently betahistine HCl was found to have certain histamine like properties.

Following the earlier reports in relation to the treatment of Ménière s disease with histamine publications concerning the effect of betahistine HCl in Ménière s disease have been presented by various authors (Hicks, Hicks & Cooley 1967 Le Pere 1967 Wolfson Myers & Schlosser 1967 Martinez, 1972)

The purpose of the present study is to evaluate not only the subjective changes but also the objective changes following drug administration in both normal and pathological subjects presenting Ménière s disease Both the cochlear and vestibular functions are analyzed and the specific aims are

1) To evaluate the effect of betahistine HCl on the function of the labyrinth in healthy volunteer subjects by comparing it to a placebo in a double blind study

2) To evaluate the effect of betahistine HCl and a placebo using a randomized double blind method for both subjective and objective effects in patients presenting Ménière s syndrome.

3) To evaluate the long term effect of betahistine HCl both for the subjective and objective results in a group of 102 patients, presenting typical Ménière s syndrome No patient presenting vertigo of other etiologies is included in this group Evaluation of the subjective symptoms as well as objective evaluation of cochlear and vestibular functions were made at different intervals during the continuance of treatment which varied from 4 months to 54 months.

4) To evaluate the presence and severity of adverse effects of betahistine HCl.

CHOICE OF SUBJECTS

In the first group the study includes 10 healthy volunteers, five males and five females, between the ages of 20 and 29 years, without history of otoneurological pathology Patients in the double-blind study as well as those in the longitudinal study include patients presenting non-equivocal Ménière s syndrome Randomization for reasons which will be discussed later on was not done There is no age restriction in this group but pregnant women were excluded.

METHODOLOGY

On all subjects both subjective and objectiv modifications were studied at regular contr visits.

The objective tests included studies of bot the cochlear and vestibular function Bot studies of the spontaneous nystagmus, as we as positional caloric and rotational stimula tions were done Several patients, having n response to caloric stimulation as used accord ing to Hallpike s technique (30 and 44) wer stimulated with ice water at 0 C. Others, hav



Fig. 1 Position of electrodes to record the horizontal movements of eyes separately technique routinely used. The vertical movement is recorded for one eye only

ing middle or external ear pathology were stimulated by cold air according to Dundas-Grant's technique.

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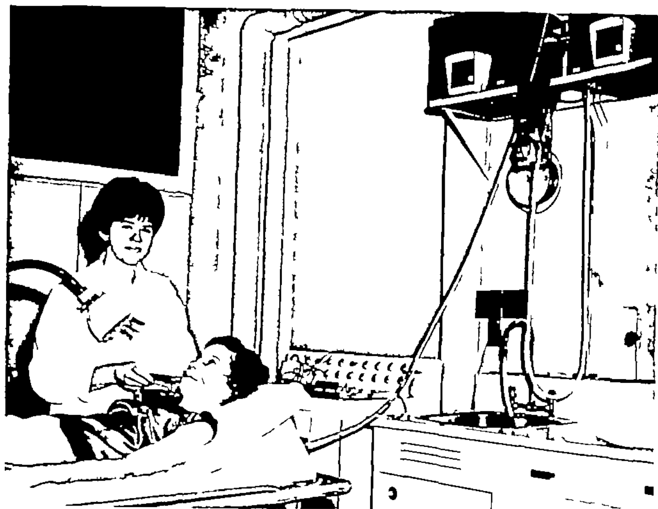


Fig 2 Caloric stimulation the patient is on a stretcher with the head flexed 30° The water in the tanks is in continuous circulation in order to keep the temperature constant at 30° and 44°C.

metry during clinical examination, record lateral gaze nystagmus. This procedure is repeated with the eyes closed, also asking the patient to keep his eyes in a central position. For positional nystagmus, we note its absence or presence If present, it is classified according to the modification of Nylen's classification made by Aschan Bergstedt & Stahle (1956)

Type I Persistent direction-changing nystagmus
Type II Persistent direction-fixed nystagmus
Type III All varieties of transitory positional nystagmus (e g. Nylen's transitory irregular transitional, paroxysmal, etc)

Caloric tests

With electrodes positioned in the same manner as for the positional nystagmus tests, caloric tests are done with the patient in a supine position, the head flexed 30° above the horizontal plane (Fig) We use the technique described by Hallpike irrigating each ear for forty seconds with water at 30° and 44°C The induced response is recorded with the eyes closed In cases of aural pathology such as tympanic perforation, the Dundas-Grant cold air technique is used. This method gives, in our opinion, a qualitative, *rather than a quantitative response*

The criteria used for analysis are, 1 duration of the response 2, velocity of the slow phase (VSP); 3 frequency 4 directional preponderance 5 labyrinthine preponderance.

The direction of preponderance is calculated in a percentage manner according to the formula already presented by Jongkees, using the VSP as the parameter *of analysis.*

The formula is as follows.

$$\frac{(1+4)-(2+3)}{1+2+3+4}\ 100\% = \%\ \text{of directional preponderance}$$

Where 1 = left ear stimulation 30°C
Where 2 = right ear stimulation 30°C
Where 3 = left ear stimulation 44°C
Where 4 = right ear stimulation 44 C

The directional preponderance is studied both for the duration and slow phase velocity parameters

The labyrinthine preponderance is also calculated in a percentage manner for the same parameters, also by the following formula, as advocated by Jongkee (1948)

$$\frac{(1+3)-(2+4)}{1+2+3+4}\ 100\% = \%\ \text{of labyrinthine preponderance}$$

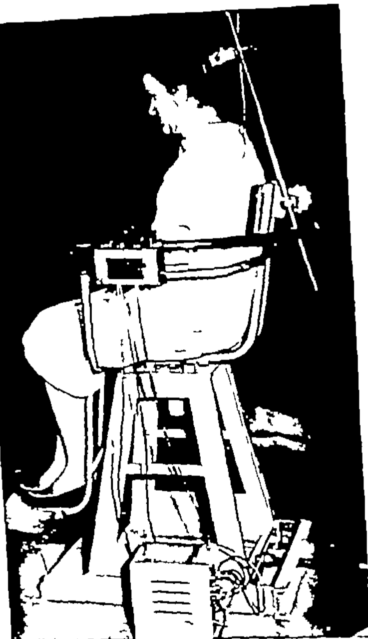


Fig 3 Rotational stimulation Controlled angular acceleration of 1 3 and 6 /s² to constant speed of 90° and sudden stop from 90°/s, for both clockwise and anticlockwise stimulations are performed at each control visit. The advantage of this stimulation is the possibility of reproducing the same exact stimulation at each control

I the evaluation of the effect of betahistine HCl in the normal and pathological subjects, the criteria used was the modification of vestibular excitability using as parameter the velocity of the slow phase

Rotation tests

Since Bárány introduced his rotation tests for the study of labyrinthine function by analysis of post-rotatory reactions, of which nystagmus was the most important, several other techniques for rotational stimulation have been proposed

Several variations of rotatory stimulation have been described since We have chosen to use that of angular acceleration. Montandon, Russbach & Pennaux (1960) introduced the study of per rotatory nystagmus, using constant acceleration and deceleration This technique

can determine the threshold of vestibular stimulation in degrees per second squared (/s²). According to Montandon et al s definition, the threshold corresponds to the speed per second squared which produces one nystagmic beat per second.

We proceed in the following manner with Ag-Ag-Cl electrodes in the same position as for the positional and caloric tests, the patient is seated in the rotating chair with his head flexed 30° (Fig 3) This gives a horizontal plane to the lateral semi-circular canal and assures maximum stimulation during rotation. The previous calibration of the recording sensitivity (20° eye movement = 20 mm of pen displacement) is re verified, using a Maddox cross, for both the hori zontal and vertical leads. In total darkness, and with the eyes open, four controlled rotations are done.

A counter-clockwise linear acceleration at a rate of 1 per second squared (1 /s²) is maintained until a speed of 90° is reached After _ min of constant speed at 90° the rotation is stopped suddenly The nystagmic response is recorded during the entire rotation and the post rotatory period. This is repeated, using a linear acceleration. These two rotations are followed by a counter clockwise (and then a clockwise) accelera tion of 3 /s² to a speed of 90° which is again main tained for two minutes. Deceleration is then begun at 6 /s This technique is a slight variation of that of Montandon et al. which accelerates and decelerates at 3 /s² and then at 6 /s² for both the counter-clock wise and clockwise rotations Montandon et al s tech nique requires two additional rotations which prolong the duration of the tests without in our opinion, providing additional information. In our technique, we obtain 1 /s² and 3 /s² positive acceleration stimulation of each labyrinth as well as a sudden stop from 90° constant speed and 6 /s² negative acceleration from both labyrinths

The parameters which we study are the following: (a) vestibular threshold, using Montandon et al s de finition of one nystagmic beat per second (b) velocity of the slow phase at stimulation of 1 3 and 6 /s² and a sudden stop

For the rotational stimulation, we used the same criteria as for the caloric stimulations to evaluate the effect of betahistine HCl, the velocity of the slow phase

DESCRIPTION OF MEDICATION

For the double-blind study of normal subjects and of Ménière s patients, the tablets were supplied by the Unimed Pharmaceutical Co Both the placebo and the active drug had the same appearance and were indistinguishable from one another

The code was made by Unimed Pharma ceutical Co the active tablets coming from the Lot 111 641 61 the placebo tablets from the Lot 19 A 001 A The code was not broken until the double-blind studies were ended. Also the medication was given in a randomized fashion by the secretary without knowledge of the clinician as to whether the patient received the drug or the placebo.

It is to be noted that a sealed envelope containing code numbers to corresponding drugs was given to the researcher This was done in case of emergency towards a drug reaction. The need did not arise to break the code be fore the end of the study

For the patients included in the long term longitudinal study medication was supplied by Unimed Pharmaceutical Co. with the clinician cognizant of the fact that he was having active drug There was no code on this drug

Group I

Every volunteer was examined by the clinician to ascertain that he did not present any ear nose and throat pathology The ear drums were examined and found to be normal in all patients. There was no history of cranial trauma, ear infection or vertiginous symptoms in all of these healthy subjects. These subjects included 5 males and 5 females the ages vary ing from 20 to 29 years of age. Audiometric tests were performed on all of these subjects and were found to be normal These audiometric tests were not repeated at the end of the study in the normal subjects, as no modifications were expected.

Following a control test of the vestibular function for the study of spontaneous nystagmus and positional, caloric and rotational stimulation each subject was given a code number which corresponds to the order of his admission on the project. Namely the first patient accepted is given no 1 the second is given no 2, etc.

He was then given one of the two medications, either betahistine HCl or the placebo in a randomized manner and advised to take his medication The posology of two tablets t i d. for 1 week before his appointment as well as in the morning and noontime on the

Table I. *Normal subjects: caloric stimulation*

	VSP	F	Dur	VSP	Fr	Dur
	Left ear 30°C			Right ear 30°C		
Control	22.4	2.1	152	21.2	2.2	145
Betahistine HCl	23.8	2.2	142	13.0	1.8	141
Placebo	19.9	2.2	133	18.9	1.8	135
	Left ear 44°C			Right ear 44°C		
Control	17.5	2.0	134	17.4	1.7	145
Betahistine HCl	17.6	2.1	144	12.9	1.9	129
Placebo	13.4	1.6	121	12.4	1.4	125

Summation	VSP	Freq	Dur
Control	19.6	2.0	144
Betahistine HCl	17.4	2.2	139
Placebo	16.1	1.8	129

Average response to caloric stimulation of 10 normal subjects with betahistine HCl, 2 pills t. d. (24 mg/day) and a placebo for 1 week
Control, pre-trial tests
VSP, velocity slow phase
Fr frequency/second
Dur duration of nystagmic response in seconds

day of his appointment. The total daily dosage was of 24 mg a day

To give more value to this normal group of subjects, all vestibular tests were made in the same period of the day as was the control test. We also advised every subject to refrain from taking alcohol during the drug-study period and to refrain from using any other concomitant drug

All of these ten normal subjects were paid for their participation in the experiment and all of them completed the experiment as scheduled

RESULTS

Group I Normal subjects

There were no modifications in this group of normal subjects with both betahistine HCl or the placebo as can be seen in the summary presented in Tables I and II.

Johnson (1969) in a personal communication dated October 2nd, 1969 stated. I have also tested Serc on normal humans and found no change in ENG from caloric stimulation.

Group II A double-blind evaluation in Ménière's patients

The original protocol included three distinct groups of subjects: (*a*) double-blind evaluation in normal subjects (*b*) double-blind evaluation in Ménière's patients and (*c*) longitudinal study in Ménière's patients.

As far as the second group is concerned in regard to the double-blind evaluation of betahistine HCl and a placebo in Ménière's patients, the protocol required a pre-treatment evaluation of the subjective and objective cochlear and vestibular function, followed by the administration in a randomized double blind manner of the placebo or drug for a period of one month, after which, following another control, a cross-over to the other medication was made for an additional month of treatment, again followed by a new control.

At the time this protocol was elaborated, the double-blind study was inserted in order to comply with rules and regulations of certain Food and Drug Administrations who suggest that double-blind studies be included in clinical trials for drugs subjected to their Department for approval in the treatment of various diseases.

However it is the author's opinion that a double-blind evaluation in patients presenting Ménière's syndrome cannot be performed adequately except under almost impossible conditions

Several reasons exist for this statement. One reason can be considered to be the presence of spontaneous remission which can occur in this symptomatology It is well known that the majority of patients can have spontaneous remission in the average of four to eight months and in certain cases for several years without any medication (Crowe, 1938 McNally & Stuart, 1955) In the author's series, *one* patient had a period of remission of 17 years.

Case history I D R., 52 year-old male

This 52-year old male consults for vertigo. In his history he states that, at the age of 10 or 12 years old, he presented objective rotatory crises with nausea and vomiting. These crises were present at the

can determine the threshold of vestibular stimulation in degrees per second squared (/s²) According to Montandon et al s definition, the threshold corresponds to the speed per second squared which produces one nystagmic beat per second

We proceed in the following manner with Ag Ag-Cl electrodes *in the same position as for the positional* and caloric tests, the patient is seated in the rotating chair with his head flexed 30° (Fig. 3) This gives a horizontal plane to the lateral semi-circular canal and assures maximum stimulation during rotation The previous calibration of the recording sensitivity (20° eye movement = 20 mm of pen displacement) is re-verified using a Maddox cross, for both the horizontal and vertical leads. In total darkness, and with the eyes open, four controlled rotations are done

A counter-clockwise linear acceleration at a rate of 1 per second squared (1 /s²) is maintained until a speed of 90 is reached. After 2 min of constant speed at 90° the rotation is stopped suddenly The nystagmic *response is recorded during the entire rotation and* the post rotatory period This is repeated, using a linear acceleration These two rotations are followed by a counter clockwise (and then a clockwise) acceleration of 3 /s² to a speed of 90° which is again maintained for two minutes Deceleration is then begun at 6 /s This technique is a slight variation of that of Montandon et al. which accelerates and decelerates at 3 /s² and then at 6 /s² for both the counter-clockwise and clockwise rotations. Montandon et al. s technique requires two additional rotations which prolong the duration of the tests without, in our opinion providing additional information. In our technique, we obtain 1 /s² and 3 /s² positive acceleration stimulation of each labyrinth as well as a sudden stop from 90° constant speed and 6 /s² negative acceleration from both labyrinths

The parameters which we study are the following (*a*) vestibular threshold, using Montandon et al. s definition of one nystagmic beat per second (*b*) velocity of the slow phase at stimulation of 1 3 and 6 /s² and a sudden stop

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It is to be noted that a sealed envelope containing code numbers to corresponding drugs was given to the researcher This was done in case of emergency towards a drug reaction. The need did not arise to break the code before the end of the study

For the patients included in the long-term longitudinal study medication was supplied by Unimed Pharmaceutical Co with the clinician *cognizant of the fact that he was having active* drug There was no code on this drug

Group I

Every volunteer was examined by the clinician to ascertain that he did not present any ear nose and throat pathology The ear drums were examined and found to be normal in all patients. There was no history of cranial trauma, ear infection or vertiginous symptoms in all of these healthy subjects. These subjects included 5 males and 5 females, the ages varying from 20 to 29 years of age. Audiometric tests were performed on all of these subjects and were found to be normal These audiometric tests were not repeated at the end of the study in the normal subjects, as no modifications were expected.

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He was then given one of the two medications, either betahistine HCl or the placebo in a randomized manner and advised to take his medication. The posology of two tablets t.i.d. for 1 week before his appointment as well as in the morning and noontime on the

animal experimentation of Martinez (1972) in the guinea pig, it is believed that betahistine HCl produces vasodilatation of the capillaries of the stria vascularis, probably capable of modifying the permeability of these capillaries and possibly altering the status of endolymphatic electrolytic composition and pressure. If such were the case, the administration of betahistine HCl in the first stage of a double-blind study could restore a normal endolymphatic system in the second trial period and the placebo would be equivalent to treating a normal cochleo-vestibular apparatus.

For these various reasons, we are giving no interpretation whatsoever to the double-blind evaluation in Ménière's which was initiated but not completed.

Because of the psychological aspects closely related to this syndrome, which was studied in detail in 31 patients by Basecqz (1969), we also did not feel justified to treat in a double-blind manner patients in a longitudinal study by substituting at certain periods of the treatment, the active drug with a placebo identical to the drug. Many of these patients who had previously been controlled by other medication for a certain period, either because of drug efficacy spontaneous remission absence of their own probable etiological factors, such as "stress" "allergy" etc could be influenced to believe that the drug had become ineffective a phenomenon which had previously been also experienced with other drugs.

Group III Longitudinal study

In the author's opinion, the only valuable evaluation of any treatment for Ménière's disease is a longitudinal study of a long-term duration Certain premises must be taken into account Among these, must be considered spontaneous remission, lack of homogeneity various possible etiological factors, randomization, as well as the psychological aspect of this disease and the doctor/patient relationship. All the patients included in this longitudinal study consisted either of private or clinic patients treated at each visit by the same physician in order to obtain as much homogeneity of treatment evaluation as possible. Each patient treated was classified by the author according to the intensity of his pathology in three categories, I, II and III. This gradation is purely subjective, probably has no value for comparison with patients treated by other physicians, but when used by the same physician, might have some value in relation to the severity of the disease in a particular patient.

For the clinical evaluation of the Ménière's patients treated, they were divided into three groups in the following manner

I The first category is composed of patients presenting vertigo of a benign nature associated with occasional fluctuating hearing loss.

II. In this category are those patients presenting a more pronounced vertigo associated with a permanent hearing loss.

III. In a third category are included advanced cases of Ménière's disease usually not responding to medical treatment. These cases are often candidates for surgical treatment. Included in this group are all the patients referred for surgery or opinion concerning surgery by ENT colleagues or neurologists or neuro-surgeons.

The longitudinal study consists of 102 patients with ENG and audiometric controls. The patients were tested before the beginning of treatment with betahistine HCl and then submitted to the treatment, with control at 1 month, 2 months, 4 months and afterwards for the longer-term evaluation, at periods of 6 months to a year

The regular controls included for the audiometry tonal, vocal, Békésy SISI audiometric tests. The vestibular test included spontaneous and positional stimulation as already described. Caloric stimulation at 30 and 44 C or Dundas-Grant technique in the presence of drum perforation and also angular acceleration at 1 3 and 6 /s and sudden stop from 90.

First of all, before the test, the patient was seen and examined by the author the severity of his disease evaluated and the symptomatology for vertigo, nausea, vomiting, tinnitus.

Table II *Normal subjects, rotational stimulation*

	1 /s	3°/s	6 /s²	St	Dur
Left ear anti-clockwise acceleration					
Control	2.3	4.5	8.0	11 4	31 7
Betahistine HCl	2.4	3.9	6.0	11.0	30
Placebo	1 9	4.5	6_	10.2	30
Right ear clockwise acceleration					
Control	2.4	4 4	7 7	13.0	39
Betahistine HCl	2.0	4.5	6 8	17 1	36
Placebo	2.5	4 6	5 7	11.5	32

1 3 6°/s² average velocity of the slow phase of angular acceleration of 1 3 6 /s
St sudden stop from constant speed.
Dur time of the nystagmic response in seconds following the sudden stop.

quency of one every week and sometimes more often They could happen at any time in the day and even at night when he would wake up with nausea and vomiting These vertiginous episodes lasted for a period of 1 / to 2 years, with no tinnitus or hearing loss during the crises. There was a complete remission of the crises for a duration of 15 years.

At the age of 55 he suddenly started to present vertiginous crises at a frequency of 3 to 4 crises a day with nausea and vomiting. When asked how many crises he presented he answered. "Hundreds, hundreds and hundreds" During that period he was incapable of doing any work and had to lie down when he had the vertiginous crises. For a period of 3 years, his wife had to work in order to compensate for his total loss of work. There was a slight left ear hearing loss noted during that period. After 3 years, the vertiginous episodes stopped suddenly with no treatment

After a complete remission of 17 years, he again started to present tinnitus in the left ear a gradual left ear hearing loss, and a sensation of fullness or pressure in that ear Eighteen months later vertiginous crises reappeared with nausea and vomiting which were still present when he consulted. This patient presenting a characteristic syndrome of Ménière had two periods of complete remission. The first one of approximately 13 years and the second one of a duration of 17 years

A trial period of 1 month must be then considered too short a period, yet, to extend these periods to several months is almost impossible and in many cases not justifiable If for example, a trial period of 6 months was instituted it is inconceivable that a patient for the sake of scientific study should be kept on a placebo drug while presenting an uncontrollable incapacitating syndrome during all that period The clinician would be morally unjustified for not treating this patient. Moreover many of these patients, in the absence of effective control of their symptomatology would either stop taking the medication or consult elsewhere for adequate treatment.

Another aspect which would seem to invalidate most double blind studies is the absence of homogeneity of the patients treated. While the anatomo-pathological manifestations of cochleo-vestibular hydrops has been well demonstrated the etiological factors still remain in the realm of hypothesis. Several hypotheses exist which seem capable of producing this picture of hydrops. The factors capable of producing these hydrops may respond to various treatments and may explain the multiplicity of treatments as well as the variations of results obtained in certain cases in which an effective treatment in one patient might be ineffective in another

This lack of homogeneity may be present not only in relation to the etiological aspect, but also in relation to the severity of the disease in patients afflicted with this syndrome.

Another aspect which must be considered is the choice of patients to be included in this double-blind study In most cases, it is impossible to include in a randomized fashion patients presenting Ménière s syndrome Many patients may be referred or may consult for a marked incapacitating disease for which either the referring ENG neurologist or physician after having tried several available medical treatments, has convinced the patient that surgery is indicated It would be difficult to include these patients in a double blind study in a randomized manner Also certain patients, because of occupational hazards social conditions or geographical location cannot be included in a randomized fashion in a double-blind study

While this objection to a double blind study in Ménière s patients may apply in a general manner to all medications, another objection exists with the use of betahistine HCl As will be explained in the discussion following the

in the left side which went from a Type II to Type I and for the right side from Type IV to a Type II. There is no significant change in vocal audiometry. This probably explains the subjective sensation of no improvement of hearing.

Vestibular test also demonstrates modifications of the slow phase with the medication.

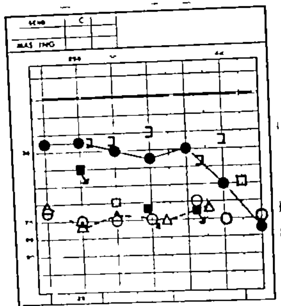
This patient is now under treatment for over 4 ½ years and was last seen 2 months ago. The vertiginous crises are now almost completely controlled and when present do not last more than 10 to 15 sec. On several occasions he stopped taking the medication. Within a few days, the vertiginous crises reappeared, only to be controlled again when the drug was re-administered.

Case history L. M. 71 year-old male, right ear Ménière's disease

This 71 year-old male was investigated for a right ear Ménière, present for the last 10 years. The vertiginous crises were frequently associated with nausea and vomiting and recently had shown a marked increase in intensity and frequency. The audiometric test (Fig. 5) showed a 50 dB neuro-sensorial loss on the right side with diminished discrimination with Type IV Békésy and a positive SISI test.

A 2 month treatment with betahistine HCl, 24 mg daily showed a marked improvement of the vertiginous problem. This patient was then seen at regular intervals for a period of up to 23 months. When seen in March '68, the patient stated that he had no more vertiginous crises. He ran short of the medication for a few weeks and the vertigo reappeared. However as soon as he resumed his treatment, the vertiginous crises again completely disappeared. There is no modification concerning the objective and subjective hearing in this patient.

Shortly after his last visit in March '68 this patient had a coronary thrombosis for which he was hospitalized in his home town and treated in an intensive manner. His cardiologist did not prescribe any betahistine HCl and after 5 or 6 days of intensive treatment, in addition to his cardiac problem, he again began to present vertiginous crises. It was only after ... weeks of continuous request by the patient that he should be given his "vertigo pill" that the cardiologist consented, in the presence of continuous vertiginous crises, to add betahistine HCl to the medication which this patient was already receiving for his cardiac pathology. A few days later the vertiginous crises were again completely controlled. This patient was seen a year after his coronary thrombosis, still taking betahistine HCl. He did not want under any consideration whatsoever another trial period of drug withdrawal.



	R.E.	L.E.
S.R.T.	80 db	44 db
DISC.	40 %	64 %
D. IN NOISE	20 %	32 %

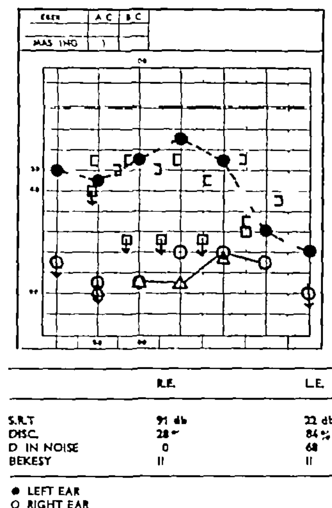
● LEFT EAR
○ RIGHT EAR

Fig. 5. Audiogram of a patient for whom concomitant medication was given with betahistine HCl. The withdrawal of betahistine HCl for a few days resulted in the reappearance of vertiginous crises.

On the basis of subjective evaluation, it is almost impossible to present convincingly whether the results are satisfactory or not. Considering the group of patients who are submitted to this therapy, were we to include only those of advanced cases of Ménière's disease classified in this study as Grade III, the percentage of good results would be quite low. Yet, in some patients in whom there was a failure of other medical treatment by other ENT specialists and who were referred for surgery but were submitted to betahistine HCl therapy for a trial period, we were able to obviate the necessity of surgery and the case of such a patient is presented.

Case history L. D. 65-year-old male

This 65-year-old patient had attacks of objective rotatory vertigo which usually lasted an hour and a half for the last 18 months. They occurred at a frequency of three or four a week. Between his attacks, he also had slight equilibrium problems of a few second duration in relation to movement of his head. This is associated to a left side hearing loss and tinnitus



	R.E.	L.E.
S.R.T	91 db	22 db
DISC.	28 %	84 %
D IN NOISE	0	68
BEKESY	II	II

● LEFT EAR
O RIGHT EAR

Fig 4 Audiogram of a patient who has been treated with betahistine HCl for over 4 / years. Several attempts at drug withdrawal were followed by reappearance of the vertiginous symptoms within a few days.

hearing sensation of fullness and headaches recorded From a subjective point of view these symptoms were graded according to their intensity for a given patient, from "0 "1" and "2 "0" being the absence of symptoms, 1" a moderate presence of the symptoms and "2" a marked presence of the symptoms. When the patients were seen these symptoms were again re-evaluated and the number was changed in relation to a given patient as to whether there was an increase or a decrease of the symptoms for that given patient The severity of the symptoms which was classified as 2" for one given patient could not be transposed as being of equal severity for another patient also classified as "2" for that symptom. An increase of a particular symptom was recorded as 3"

The results were studied for:

1 The results concerning the clinical evaluation for each of the seven symptoms recorded and graded.

2. The objective modification of the audiometric tests.

3 The objective modification of the response following the various vestibular stimulations.

In our series of control tests, we have patients who have now been taking the drug for periods of over 4 ½ years. One interesting aspect of the clinical symptomatology is the frequent mention by several of these long-term patients of the reappearance of the symptoms of Ménière s disease after a few days of drug withdrawal. Once they start taking the drug again, there reappears a complete disappearance of the symptoms Since we have already enunciated our disbelief of the possibility of doing a double-blind study during longitudinal studies in Ménière s patients by substituting a placebo this drug withdrawal seems to be of a significant value.

Case history J C 62 year-old male

This patient first consulted for objective rotatory vertigo with nausea and occasional vomiting. The crises were of a 10 to 15 min duration at a frequency of two to six crises per day for several months Six years previously when these symptoms were first noted the patient had a right ear tinnitus. Three years before consultation, investigation elsewhere had shown a marked neuro-sensorial hearing loss in the right ear associated with marked problems of discrimination Medical therapy previous to consultation did not control the vertiginous crises. For the last few months, he had noted an associated left sided tinnitus and hearing loss There was a 4 dB neuro-sensorial loss in the left ear

After two months of treatment, with betahistine HCl, 24 mg per day we note a marked diminution of the intensity of the crises and of their frequency The duration being of to 3 min compared with 10 to 15 min previously at a frequency of 2 to 3 crises per day The patient notes that it does not feel necessary to lay down at the time of the crises and there is also a slight diminution of the tinnitus, but no objective improvement of the hearing loss. Tonal audiometry demonstrates a marked improvement.

The pre treatment average loss of 4 dB was now 17 dB (Fig. 4). Békésy test also shows improvement

Dr Robert-A Bertrand
Montréal.

Che docteur

À ma visite précédent (fin d mai ou juin 1968) vous viez recommandé d vou revoi au bout d une année

Durant c temps j i pris l médi ment Serc qui améliore ma condition lorsque j néglige d prendre ces pilules j i d vertig ré quelque jours Mon audition sembl stabilisé

Il y pa d hangement notable, à ma connai sanc sera t il nécessaire de vous revoir? Si oui, veuillez indique un rendez- ous au moment qui vous convient l mieux

Bien à vous

Fig 7 Original letter of patient in whom the symptomatology recurs with drug withdrawal.

excitability it is to be noted that several patients showed, even following a long-term treatment, no modification of the vestibular response. Some presented from the beginning a diminution of the vestibular excitability

For the audiometric controls as shown in Fig. 10 the improved hearing was usually of a transitory nature.

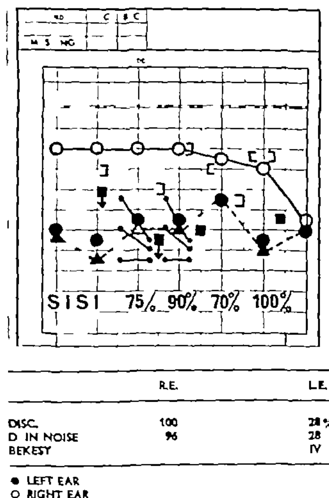
A long-term evolution is shown here for a period of 18 months, for both the vestibular and cochlear evolution in a 40-year-old female who was first referred in 1964 for bilateral Ménière and had been submitted to various treatments in the years 1964 1965 and 1966 by the author These included thiethylperazine (Torecan Sandoz) (Bertrand, 1966) in a double blind study and long-term evolution with no modification whatsoever of the hearing and persistence of desequilibrium problems. She was also treated with diphenidol (Vontrol Smith, Kline & French), also with no modification whatsoever of the cochlear function and persistence of the vestibular symptomatology

The audiogram following treatment with diphenidol was made on the 21st of June 1966, demonstrating a bilateral neuro-sensorial hearing loss, in the neighborhood of 55 dB in the left ear and 65 in the right ear Following the beginning of treatment with betahistine HCl, there was a marked improvement in hearing which persisted for 5 months after treatment in the right ear and varied slightly in the left ear The last audiometric control, 18 months after the beginning of treatment, demonstrates hearing improvement which did not persist consistently but is still present somewhat, especially for the left ear This pattern of initial improvement followed by secondary stage of reversal to the pre-treatment level for the hearing function, has been frequently observed.

As can also be observed (Fig. 11) the discrimination score which was below 60% for the right ear and 75% for the left ear was improved and remained so, after eighteen months of treatment. We can compare the fact that the improvement which is noted in the discrimination score in the left ear has persisted just as the improvement in tonal audiometry whereas the right is again showing a slightly diminished discrimination score On the same diagram, we can see for the corresponding dates the results of the Békésy audiometry which reverted from a Type II gradually to a Type I in both ears.

The vestibular evaluation for this patient which extends for a period of 3 years, demonstrates that from a hyporeflective response, we obtained an increase of the vestibular response, and after a while this response is gradually decreasing.

The same phenomena have been observed in



	R.E.	L.E.
DISC.	100	28 %
D IN NOISE	96	28
BEKESY		IV

● LEFT EAR
O RIGHT EAR

Fig 6 Audiogram of a patient referred for surgery by an ENT specialist in whom several medical treatments had failed to control the vertiginous attacks, and for whom surgery was obviated by medical treatment with betahistine HCl.

(Fig 6). He had been treated with several medications without improvement. This patient was referred for surgical treatment by his ENT specialist.

A trial treatment with betahistine HCl at a posology of two tablets t i d. (4 mg) was attempted for months During the first month of treatment, he noted only four attacks of vertigo of a very decreased intensity and duration. The first attack lasted about 10 min and the second one about 1 min without nausea and vomiting However he presented a concomitant problem of fatigue when reading The third attack was only of 4 or 5 min duration while the last one was of 30 min with nausea and vomiting There was also a marked decrease of tinnitus, sensation of pressure and a subjective improvement of hearing Clinically this patient who presented a very marked indication for surgery was considered sufficiently improved to continue medical treatment.

This patient has now been treated continuously with the drug for a period of 36 months. On a few occasions, he stopped taking the medication and he noticed a re-occurrence of his equilibrium problem and small vertiginous crises. These disappeared upon re-administration of the drug

On the other hand, had only patients presenting the early stages of Ménière s disease graded in Group I" by the classification used in this study be included, the results would probably be of 91% positively cured patients, out of which a great majority could be imputed to spontaneous remission, rather than to the active drug

We must then assume that the clinical evaluation in longitudinal study can only be of an approximate certainty and only remission of long duration throughout several years with increased symptomatology following drug withdrawal, really seems to demonstrate an active effect of this drug To emphasize this point, I would like to present a letter (with its translation) from a patient who has now been taking this drug for a period of over 3 years and 8 months (Fig 7)

Many patients, as shown for a particular patient (Figs 8 *a*, *b* *c*) in the early stage presented an increase of vestibular response which we attributed, following the studies and work of Kubicek & Anderson (1967) and Martinez (1972) to a vasodilatatory effect, probably in the region of the stria vascularis which most likely modifies the permeability of the capillaries, thereby modifying the status of the endolymphatic system

While we have already discussed this modification in the early stage of the disease (Bertrand, 1967 1971) we noticed, using a long term longitudinal study with ENG control, that there appeared a second stage of hyporeflective response (Figs. 9 *a* *b*) However even though the objective response became hyporeflective in *the second stage of long term evaluation* the initial favorable results of subjective improvement usually persisted.

While several patients presented this pattern of initial vestibular response increase followed by a secondary stage of diminished vestibular

Dr Robert-A Bertrand
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Il n'y a pas de changement notable, à ma connaissance sera-t-il nécessaire de vous revoir? Si oui, veuillez m'indiquer un rendez-vous au moment qui vous convient le mieux

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Fig 7 Original letter of patient in whom the symptomatology recurs with drug withdrawal.

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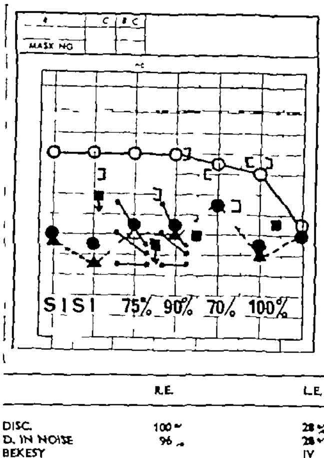


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While several patients presented this pattern of initial vestibular response increase followed by a secondary stage of diminished vestibular



Fig 8 The increased response is also noted following sudden stop from constant speed of 90° (reproduced from *Laryngoscope* Vol. 85 p 893 June 1971)

of the cases in which it was observed. Referring again to the patient whose audiometric improvement is demonstrated in Figs 10 & 11 this patient had been treated previously because of the severity of her disease for the last three years with different drugs and had had regular audiometric controls, and at no time did we notice before the administration of betahistine HCl an improvement of hearing

SUBJECTIVE RESULTS

The subjective symptomatology was studied for the symptoms of vertigo, nausea, vomiting, tinnitus, hearing, sensation of fullness or pressure and headaches. We included in our summarized results the 62 patients who had also concomitant medication during the period of the long-term longitudinal evaluation. While these patients probably benefited from this concomitant medication, it is believed that the therapeutical effect could have been derived from the betahistine HCl The aim of our treatment was not only to evaluate betahistine HCl, but also to treat the patient. To this effect, in long-term evaluation, patients frequently are given concomitant medication, usually in the form of sedatives or tranquilizers

Added to the 40 patients for whom, to our knowledge, no other medication capable of influencing the vestibular response was administered, our long-term subjective evaluation includes an additional 62 patients, for a total of 102.

The author's gradation of patients, while subject to criticism and probably having no real scientific value, nevertheless led to some interesting conclusions, as can be seen in Table III. It is noted that patients graded as I, that is those in the early stage of the disease in whom the hearing loss is fluctuating and transitory but to be included had been demonstrated at least once by audiometry responded in a favorable manner in about 91% of the cases. Speculation can be made as to whether these patients are indeed Ménière s patients or whether they presented spontaneous remissions.

In those graded as II, there is a decrease in the favorable results, whereas in those patients graded as III by the author the results are quite different as those obtained in Group I Nevertheless, certain patients, graded as III, an example of which an audiometric test can be seen in Fig. 6 were controlled with the medication. It is to be noted that this patient as well as several others referred by ENT specialists specifically for surgery and that

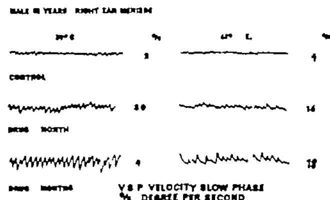


Fig 8 a Gradual increase of the intensity of the response to caloric stimulation during two months of treatment with betahistine HCl 4 mg/day (reproduced from *Laryngoscope* Vol *85* p 892, June 1971).

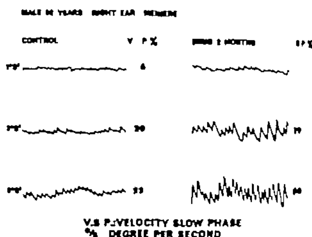


Fig 8 b Same patient as demonstrated in Fig. 1 in which an increase of response to angular accelerations of 1 3 6 /s² is present after months of treatment (reproduced from *Laryngoscope* Vol. *85* p. 893 June 1971).

the analysis of the vestibular speed of the slow phase for both ears even though one ear seems to recuperate. The vestibular speed of the slow phase shown here is the summation of the speed obtained for each ear at 1 3 and 6 /s² and that of a sudden stop from 90 There is almost a similarity of the increase of response between these two tests and the improvement of response for both the caloric and vestibular stimulations for the vestibular part of the inner ear apparatus, similar to that observed for the cochlear apparatus (Fig 12 *a b*).

While the presentation of individual patients *in Ménière's syndrome may be misleading* this marked modification of objective tests as already described can become of significant value when a larger group of patients is studied

The summation of 40 patients[1] out of 102 subjected to this study demonstrates for the caloric stimulation when dissociating right and left pathological ears and in cases of bilateral pathologies when including both pathological ears, a tendency in the early stage of an increase of the vestibular response using as criteria of analysis the average velocity speed of the slow phase in the 10 sec period of maximal response followed by a gradual decrease. The same phenomenon is observed following rotational stimulation (Fig 13) more reliability can be given to the responses obtained following rotational stimulation due to the fact that the same precise and known stimulation can be given repeatedly whereas several factors may modify the caloric stimulation

[1] For this objective evaluation, patients having had concomitant medication capable of modifying the response are not included The reader is referred to Bertrand (1971) for more details.

AUDIOMETRIC RESULTS

Subjective and objective modifications of the cochlear function were noted in several patients. Many patients presented as already seen in Fig 11 an objective improvement of the cochlear response but in most patients in whom this improvement was noted, it usually was of a transitory nature with the exception perhaps of the results of certain tests such as discrimination In these function tests the improvements were frequently of longer duration and in some cases are still persisting two or three years following the beginning of treatment

One of the main characteristics of Ménière's syndrome is fluctuation of hearing as already enunciated by Ménière especially in the early stage of the disease. Nevertheless, we believe that this drug could have initiated the occasional hearing improvement noted in several

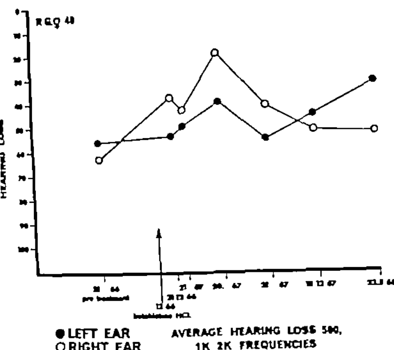


Fig 10 Modifications of audiometric tests with betahistine HCl in patient who had showed no modification for the last 3 years

tients, we recommend administration prior to meals.

Two patients presented complications in the nature of a skin rash (Fig 14 *a b*) this disappeared following drug withdrawal Occasionally a patient may complain of increased symptomatology usually related to an increase of the tinnitus or headache, as already discussed in the results of the subjective evaluation

POSOLOGY

The posology in the initial stage of treatment was one tablet (4 mg) t i d Because of the non-effectiveness in certain patients, an increase of the posology to two tablets t.i.d. (24 mg) was tried and this seems to us to be the more effective dosage An example of the effect of posology variation can be seen in Fig 15

Certain patients who have been using this medication for two or three years will reduce their daily dosage to 16 12 or 8 mg or proceed to complete withdrawal on their own, only to again increase the posology up to 24 mg if the symptoms recur After several months of treatment, gradual weaning is frequently attempted, and those presenting a recurrence of the symptoms are again given medication, usually of 24 mg daily Certain patients, as the one whose case history has been presented (J C.) have attempted at different intervals to stop the medication only to see the symptoms reappear This particular patient has now been taking the medication for over 4 1/2 years, has tried on several occasions to stop taking the medication, but this to no avail. The symptoms would reappear within one week and would always be controlled again after one or two weeks of treatment. He does not want to try again another period of withdrawal.

DISCUSSION

The evaluation of medical treatment of any kind for Ménière's disease is a very difficult proposition. We are faced with the problems of spontaneous remission lack of homogeneity

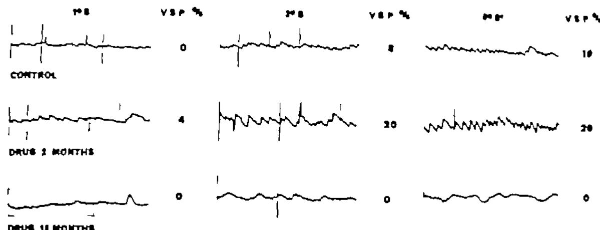


Fig 9 a Rotational stimulation at 1 3 6 /s² in a 47-year-old male presenting right ear Ménière treated with betahistine HCl, 4 mg/day the long term evaluation demonstrated that the initial increase of the vestibular response was of transitory nature.

betahistine HCl was given a pre-surgical trial and occasionally obviated the need for surgery

The results of the 102 patients for the evaluation of the various symptoms are presented in Table IV Most of the patients (24) that showed no improvement were subsequently operated Certain patients complained of increased tinnitus or headaches with the medication and such increase disappeared on drug withdrawal or reduced posology

SIDE EFFECTS

In our series, patients having gastric disorders usually were not given betahistine HCl However it was noted that patients occasionally were referred with gastric pathology and were already taking this medication with no ill effect We do not consider unless acute gastric pathology exists that it is a contra-indication to use this drug However in all of our pa

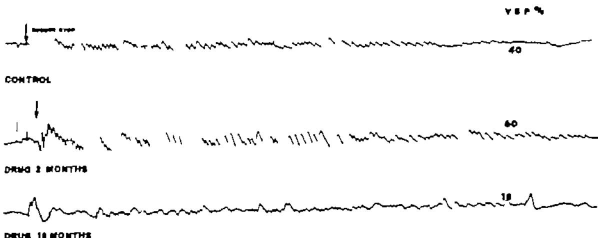


Fig 9 b The same pattern is also noted following a sudden stop from a constant velocity of 90°/s.

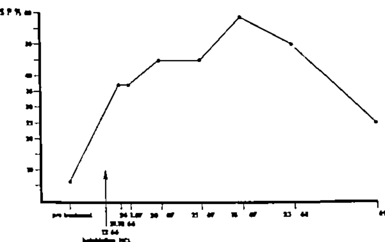


Fig. 12 a. Summation of vestibular speed of slow phase at 30° and 44°C for right and left ears

Fig. 12 b. Initial increase of vestibular response following rotational stimulation followed by a secondary stage of response decrease (reproduced from *Laryngoscope* Vol. 85 p. 894 June 1971).

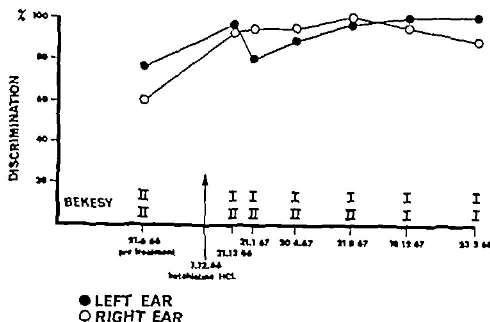


Fig 11 Evaluation of discrimination score and Békésy audiometry for patient whose tonal audiometry is shown in Fig 10.

various etiological causes and the absence of randomization The psychological and sociological aspects which can be added on to these characteristics of the study further complicate the project This last aspect is given great emphasis in our evaluation.

In this presentation we have shown our results in relation to modification of the subjective symptomatology and responses to tests of cochlear and vestibular functions. While the period devoted to this is yet too short since our longest treated patient has only been under treatment for 4 1/2 years, to have conclusive *definite results, there seems to exist a definite* pattern of response to both the vestibular and cochlear function tests.

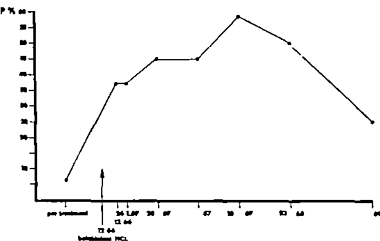
The results of modification of the subjective symptomatology seems related to the severity of the disease being more *effective in patients* presenting what can be considered early stages of Ménière s syndrome whereas the effectiveness of the drug diminishes as the severity of the disease increases.

As far as the vestibular function is concerned there seems to exist a pattern of an initial increase of vestibular response to both *caloric and rotational stimulation* using the *velocity of the slow phase as the parameter of* analysis This initial increase has been noted in individual patients and a computerized summation of 40 patients out of the 102 included in this study in whom no other concomitant medication was given as far as could be ascertained by the author demonstrates this tendency to initial vestibular response increase (Fig 13) Wilmot (1972) has just presented his initial results in 11 patients in a three month study while using angular acceleration each patient had an increase of the vestibular speed of the slow phase

*A longer time study however seems to dem*onstrate a secondary stage of vestibular response decrease We have no explanation yet to give for this secondary stage of vestibular response decrease However this is also present, but less marked for the audiological aspect

When the initial increase of vestibular response was *first noted as in the patient de*scribed in Figs. 8 *a b c* who happened to be the third patient in our series, we stated in a letter to the pharmaceutical company (Bertrand, 1967) As I have stated to you since the very beginning when I have started using this

R G Q 40



Summation of vestibular speed of slow phase at 30° and 44°C for right and left ears

Fig 12 a. Summation of vestibular speed of slow phase at 30° and 44°C for right and left ears.

R G Q 40

L E

R. E.

Fig 12 b Initial increase of vestibular response following rotational stimulation followed by secondary stage of response decrease (reproduced from *Laryngoscope* Vol. 85 p 894 June 1971).

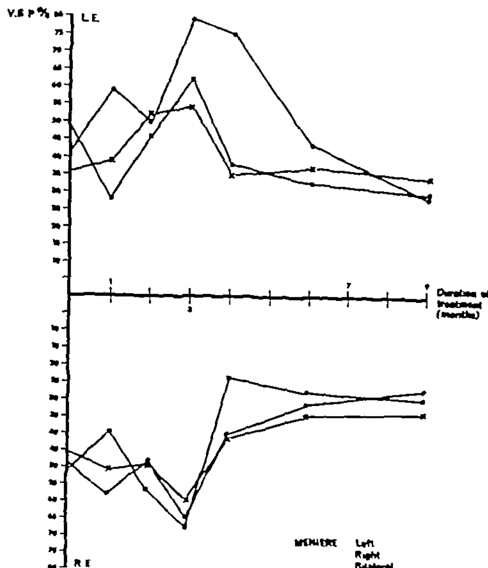


Fig 13 Average response of summation of VSP following rotational stimuli for pathological ear or ears during a 9 month period for 10 patients in whom *no other concomitant* medication or treatment were given (reproduced from *Laryngoscope* Vol 85 p 895 June 1971)

drug, I believe that the mode of action of betahistine HCl is not that of suppression or decrease of vestibular response as is the case in other drugs which I have studied, such as thiethylperazine, diphenidol or dimenhydramate. In all of these drugs, a marked decrease of the vestibular response was noted in both the normal subjects studied according to the double-blind technique as well as in the pathological subjects." And further on In Ménière's patients presenting as a rule an hyporeflective response we noted in many cases a clinical subjective improvement or disappearance of vertigo and at the same time, there seemed to be an increased response to the various vestibular stimulations "

Following these statements which were made in the initial stage of the use of betahistine HCl, two other researchers presented data concerning the use of betahistine HCl in animals.

Kubicek and his collaborators demonstrated an increase of the blood flow of the basilar arteries of dogs and hypothesized that this also resulted in an increase of the circulation in the labyrinthine artery

Martinez has just presented his findings that the use of betahistine HCl in a proportion of two tablets t.i.d. in a 75 kg man, increases the blood flow of the stria vascularis in the guinea pig within five minutes of intra-gastric administration and is accompanied by a tonic vasodilatation which lasts over an hour When betahistine HCl is administered intravenously

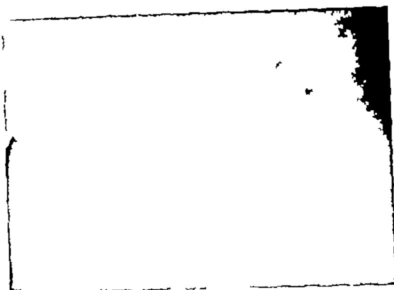


Fig 14 (*a*) Skin rash noted in a patient following administration of beta histine HCl, 24 mg daily for 1 month.



(*b*) Three weeks after drug withdrawal, the lesion was greatly diminished and had completely disappeared a few weeks later

Table III *Evolution of the symptom of vertigo in relation to severity of the disease*

Grade	No of pats	Controlled	Partially controlled	No improvement
I	11	10	1	0
II	49	28	19	2
III	42	5	15	22
	102	43 (42)	35 (34)	24 (23)

Martinez noticed an immediate marked vasodilatation, an increase of blood flow and capillaries not visible before administration of the drug were seen after such administration. This modification of the circulation of the stria vascularis as observed in the guinea pig can, due to the marked capillary vasodilatation probably lead to the modification of the permeability of these capillaries and thereby modify the endolymphatic pressure Personal communication of a preliminary study in this direction by Martinez seems to concur with this possibility

Suga & Snow (1969) recorded cochlear blood flow changes for various vasodilating drugs and some related agents, using a four electrode impedance plethysmograph. They demonstrated that betahistine HCl, at a posology of 0 01 to 0 4 mg per kg of body weight produced a cochlear blood flow increase in all 14 measurements on 13 guinea pigs The mean value and standard deviation were 224 ± 128 % of the control value, and the increase lasted more than 30 min

This modification of the circulation of the inner ear resulting in an increased blood flow as demonstrated by Martinez (1972) and Suga & Snow (1969) in the guinea pig, is assumed as also being present in man, capable of modifying the circulation in the stria vascularis, altering the capillary permeability and modifying the endolymphatic status. These modifications could then explain the results obtained in our longitudinal study thereby demonstrating that betahistine HCl is an effective drug.

CONCLUSIONS

1 Betahistine HCl seems effective in controlling the symptomatology of Ménière's syndrome or disease, especially in the early stages of the disease.
2. Many patients present transitory improvement of hearing in the early stage of treatment.
3 Objective vestibular function tests demonstrate an increase of the vestibular response in the initial stage of treatment followed by a secondary stage of vestibular response decrease.
4 With the exception of two patients having minor skin rash which disappeared following drug withdrawal, no major untoward complications were noted.
5 The effectiveness of this drug in certain cases of advanced Ménière's disease referred for surgical treatment has led us to a trial treatment period on all patients for whom we contemplated surgery

Table IV *Long-term evolution of symptomatology*

Symptom	No of pats presenting symptom	Completely controlled	Partially controlled	No improvement	Worse
Vertigo	102	40	58	4	0
Nausea	70	30	14	26	0
Vomiting	44	18	8	20	0
Tinnitus	102	20	32	46	4
Audition	98	8	20	68	2
Fullness	64	12	18	34	0
Headache	22	1	0	18	3

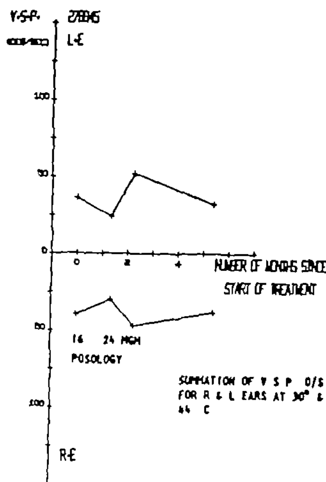


Fig 15 In certain cases in which there was no modification of the symptomatology or of the objective response, an increased dosage produced the pattern usually observed.

SUMMARY

Betahistine HCl was studied to evaluate its effect 1) in normal subjects and 2) in patients presenting Ménière s syndrome The subjective modification of the various symptoms of this syndrome as well as modification of audiometric and vestibular function were studied in 102 patients for periods of up to 4 ½ years.

A double-blind evaluation of ten normal patients with betahistine HCl and a placebo did not show any statistically significant modification of the vestibular response

The subjective evaluation in 102 patients seems to indicate that the drug is more effective in the early stage of the disease Audiometric tests frequently demonstrated improvement of hearing in the early stages, but as a rule this improvement was of a transitory nature

Vestibular function tests, in patients who had no concomitant medication capable of modifying the vestibular response demonstrate a frequent increase of the vestibular response in the early stage of treatment followed by a secondary stage of vestibular response decrease.

No untoward complications were noted in a period of 4 ½ years in 102 patients, except for a skin rash which disappeared when the medication was stopped

Following the work of Martinez (1972) and of Suga & Snow (1969) in the guinea pig, it is hypothesized that modification of the symptomatology in audiometric and vestibular response are due to modifications of the circulation at the level of the stria vascularis.

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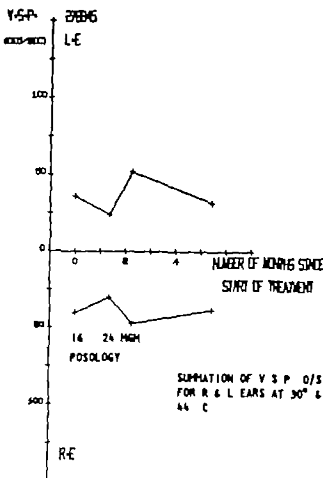


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Table I. *Information on the age, sex, complaints, disease duration and past history of the patients in betahistine study*

Patient	Age	Sex	Duration of disease (years)	Major complaints	Previous illness
1. v. d. M.	60	F	3	Tinnitus	Atopic eczema, bronchial asthma
2. Di.	36	F	3	Tinnitus, headache	Migraine
3. Em.	54	F	5	Vertigo	Gastric ulcer, essential hypertension, migraine, rheumatoid arthritis
4. Co.	50	M	5	Tinnitus, vertigo	—
5. v. d. W.	25	M	6	Vertigo	Migraine, epilepsy
6. Spi.	39	M	8	Vertigo	Bronchial asthma
7. Hu.	39	F	10	Vertigo	Bronchial asthma, pulmonary tuberculosis, sciatica
8. Bo.	51	F	18	Vertigo, tinnitus	Allergic reactions
9. An.	47	F	19	Vertigo	Alopecia diffusa, migraine
10. Ja.	51	M	26	Tinnitus	—

were not included into the study simply because there had been an exacerbation of their symptoms.

All patients were informed that they would receive a new and active drug, unknown to them they were given a placebo for the first 2 weeks of the study. After 2 weeks they were reassessed in the outpatient clinic after which they received betahistine. The first 5 patients started with 16 mg daily, later it was decided that a higher starting dose of 24 mg daily should be employed. If after 6–12 weeks at a particular dose the response was considered unsatisfactory the dose was increased, in one patient successive increases continued, to reach a daily dose of 64 mg. Throughout the trial no other drugs were given for Ménière's disease. But 1 patient with essential hypertension who had congestive cardiac failure received lasix and digitalis at intervals during the study.

At the first and each subsequent follow-up visit the patients were checked for nystagmus and Romberg's sign, the eye fundi were examined and the arterial blood pressure was measured in the sitting position after 30 min of rest. At intervals, throughout the trial pure tone audiograms were performed, these were not regularly spaced.

RESULTS

After starting the trial patient no. 1 (v. d. M.) who had shown no response to betahistine, was thought to have an acoustic neuroma. This diagnosis was confirmed and she was thereafter excluded from the study.

In this report will be presented only the results on the major symptoms, vertigo and tinnitus. The results of audiometric examination will also be discussed.

Patient's daily recordings

The information from these daily records involves more than 10 000 individual recordings. The results of all of these recordings can be illustrated graphically. The results of patient 1 (v. d. M.) who had an acoustic neuroma are not given. Some of the patients had already kept personal records of the severity of their symptoms before entering the trial, indeed one of

Proceedings of the Symposium on Ménière's Syndrome Zandvoort September 3 1970

A STUDY OF THE EFFICACY OF BETAHISTINE IN MÉNIÈRE'S SYNDROME

O R Hommes

From the Department of Neurology Radboud University Hospital Nijmegen The Netherlands

INTRODUCTION

Several reports have described the use of betahistine in the treatment of "Ménière's Syndrome [1] This study was designed to assess the effect of the drug on the daily course of the disease during a period of at least 6 months. Such a detailed report on the long term daily symptoms of this condition has not to the best of our knowledge, already been reported in any study with any form of therapy for Ménière's Syndrome.

MATERIALS AND METHODS

The patients

Included in this study were 10 patients who had suffered for a minimum of 3 years from Ménière's Syndrome (Table I) By Ménière's Syndrome is meant a chronic progressive disease characterized by repeated troublesome attacks of vertigo and tinnitus associated with progressive hearing loss. There may have been additional symptoms of headache nausea and vomiting The diagnosis was independently agreed upon in the department of neurology and the department of otorhinolaryngology at the Sint Radboud Hospital (Table II) All patients had audiograms which were consistent with the diagnosis and caloric tests Most, but not all patients had other vestibular function tests (rotating chair) All patients were subjected to a thorough neurological examination including radiographs of the internal auditory meatus and lumbar puncture In 4 of the patients, 1 (v d. M), 4 (Co), 5 (v d. W) and 6 (Sp), internal carotid angiography was also performed All patients had been deemed *failures of medical treatment. The remaining* inclusion criteria for this study were that their symptoms had to be invalidating progressive and so frequent or persistent that they would produce a reasonably high score in daily reporting. It was in addition most important that all of the patients should be sufficiently intelligent and co-operative to maintain a daily written chart on the frequency and severity of each of their symptoms for at least the first 6 months of the trial.

These multiple references have an asterisk against them in the list of references.

METHOD OF ASSESSMENT

Before starting the trial it was explained to each patient how to keep a daily symptom score record They were also asked to record daily the severity in five degrees of the symptoms vertigo tinnitus, nausea and vomiting, deafness, ear pain and headache All of the patients had some persistent daily symptoms as an inclusion criterion for the trial, so the highest score was given for the occurrence of a symptom in sudden more severe exacerbations (Table III)

In addition, the physician kept a separate record of the patients symptoms as reported at each follow up interview Not until the physician was satisfied that a patient fully *understood the scoring system was that patient* permitted to enter the trial

TREATMENT SCHEME AND FOLLOW-UP

The time of entry into the trial was determined by the date of the routine attendance at the neurology outpatient clinic and not by the severity *of the patients complaints. Patients*

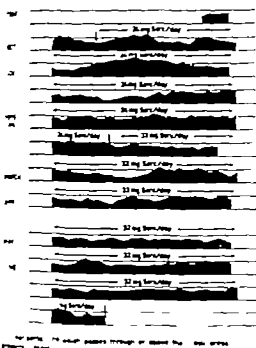


Fig. 1. Pat. 5 (d. W.). A diagrammatic representation of the total daily symptom score throughout the study. Each daily score was taken from the patient calendars. The horizontal line which passes through or above the black areas represents score of 5.

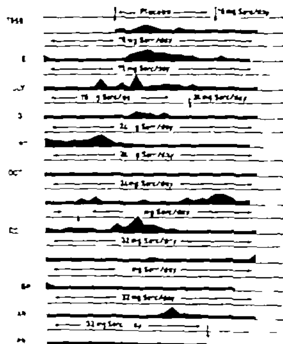


Fig. 2. Pat. 7 (Ha.). A diagrammatic representation of the total daily symptom score throughout the study. Each daily score was taken from the patient calendars. The horizontal line which passes through or above the black areas represents score of 5.

Vertigo, total scores for eight patients $p < 0.05$

Tinnitus, total score of nine patients $p = 0.05$

This analysis excludes the two weeks results because data were not available at this time from two patients because the physician was absent. In the statistical analysis the results of patient 4 (Co.), were included as being unchanged at 26 weeks, 40 weeks and the end of the trial.

Results of audiograms

Examination of the audiograms did not demonstrate that ny consistent improvement in hearing had occurred during the study nor was there clear indication that the progression of hearing los had been influenced. Preliminary evaluation of the results did suggest that the hearing improved in most patients during the first few months of betahistine treatment, especially at lower frequencies, but as no audiograms were performed on two subjects who had had unilateral labyrinthectomies and the audiograms were not regularly spaced, no attempt has been made to base any conclusions on these results. One patient (no. 5) showed an improvement in one ear of the order of 50 dB mean hearing loss at frequencies 500 and 1 000 Hz during the first months of treatment, after 6 months this improvement was still maintained. In the other ear there was an initial improvement of 20 dB at those two frequencies but 6 months later a further audiogram demonstrated that the hearing loss had returned to its original level.

Effects on social activity

Table VII shows the previous occupation of the patients in this study and the effects of

Table II *Method of confirmation of the "diagnosis" of Ménière's syndrome*

1 History
2 Audiograms
3 Caloric tests
4 Vestibular function tests—rotating chair (not all pats.)
5 Complete neurological examination
6 Radiography of internal auditory meatus
7 Lumbar puncture
8 *Internal carotid angiography (not all patients)*

them had kept daily records since 1965 and these records were also available for analysis. The total symptom scores were represented graphically Figs. 1–4 represent the total scores from 1 patient who was a failure of treatment (no 5) and 3 patients who responded (nos. 7 9 and 10)

All but two of the patients showed a marked decrease in the total symptom scores during the first 6–12 months after starting betahistine. Closer examination indicates that in the successful patients was a fall in the baseline the height of the symptom peaks was reduced and a decreased incidence of symptom peaks running together indicates a reduction in the duration of the episodes of increased symptoms.

Physician's assessment

The results from the physician's assessment demonstrated a trend which was similar to that seen from the patient's own record keeping During the first 6 weeks of treatment although some patients improved the results were not dramatic between the 10th and 20th week of treatment improvement in the symptoms vertigo and tinnitus became much more clear This improvement continued to increase during the subsequent 20 weeks and when the patients were re-assessed before making this report, this improvement could be seen to be maintained.

Two patients did not respond to betahistine one of these (no 4) (Co) had very severe persistent symptoms, and although there was a marked decrease in the symptoms nausea and vomiting in the view of the absence of change in tinnitus and vertigo the treatment with betahistine was stopped after 29 weeks the other patient (no 5) (v d W) had shown no consistent improvement after 44 weeks of treatment.

Tables IV and V show the change in the number of patients showing a consistent improvement on betahistine as the trial progressed The date of the final assessment was between 44 and 86 weeks after entering into the trial.

From these tables it can be seen that in 6 patients there was a consistent improvement in vertigo one was unchanged and one was worse at the time of making this report Six patients demonstrated consistent improvement in tinnitus and 2 were unchanged. For both symptoms the change in number of patients who improved is statistically significant

Table VI illustrates the total symptom scores for vertigo and tinnitus at intervals throughout the trial This type of scoring system belittles the extent of any change which is seen, for example a change of only one figure in the individual score for tinnitus could mean the difference between a patient being incapacitated at home or actively working This is better understood when it is considered that an improvement in a particular symptom was usually paralleled by an improvement in one or more of the other symptoms.

The trends in total score values were tested for statistical significance using Spearman's test of rank correlation

Table III *Patient's scoring system details of the complaints assessed and the method of scoring*

Complaints (subjectively assessed)	Scoring system	
Vertigo	No complaint	(0)
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Deafness	Serious complaints	(3)
Ear pain	Exacerbations in attacks	(4)
Headache		

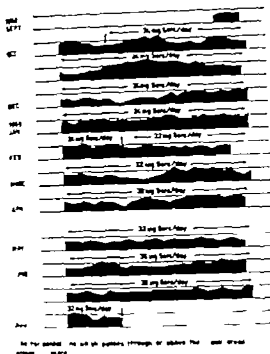


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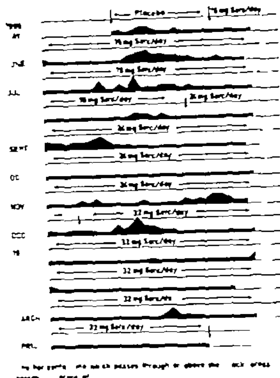


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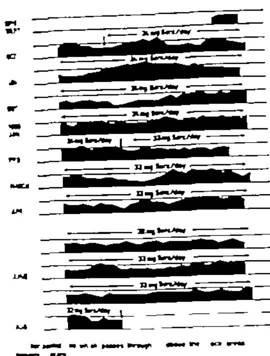


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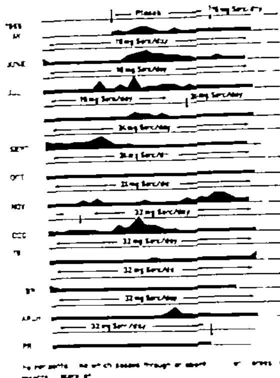


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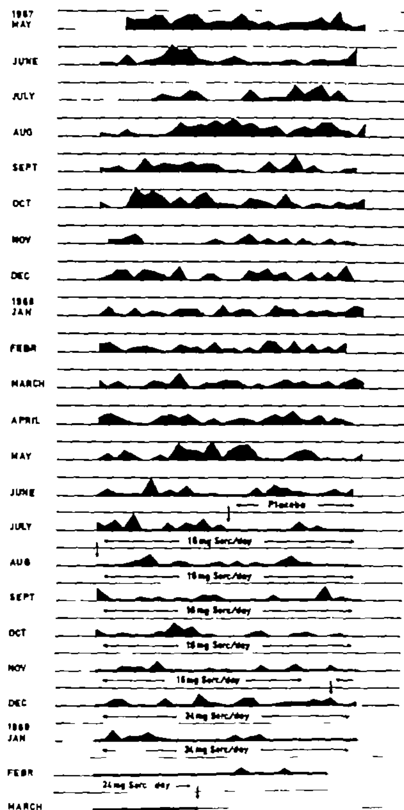


Fig. 3. Pat. 9 (An.) A diagrammatic representation of the total daily symptoms score throughout the study. Each daily score was taken from the patient calendars. The daily symptom scores during the 14 months before starting treatment with Serc are also shown. The horizontal line which passes through or above the black areas represents a score of 5.

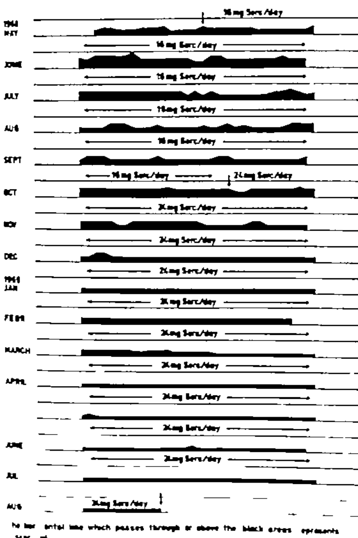


Fig. 4. Pat. 10 (Ja.). A diagrammatic representation of the total daily symptom score throughout the study. Each daily score was taken from the patient calendars. The horizontal line which passes through or above the black areas represents a score of 5.

treatment on their ability to work. The total symptom charts of patients no. 5 (failure), 9 and 10 illustrate the daily symptoms in 2 of the patients who respond compared with 2 patients who did not respond to treatment. The change in disturbance of daily life can be clearly seen in patients 9 and 10.

Dose of betahistine

The maximum dose of betahistine employed at the time of making this report is 64 mg daily; the minimum dose for any patient at this time is 24 mg daily.

Side-effects

One patient (no. 6) (Spl.) had an exacerbation of bronchial asthma which lasted for 2 weeks when he first received the active tablets. This patient had had asthma before it become apparent that he had Ménière's Syndrome; this was the first attack that he had had since the latter diagnosis was made 8 years previously. After 2 weeks of betahistine treatment the exacerbation subsided and no further episodes occurred during the subsequent 56 weeks of treatment. Three other patients had a past history of allergic disorders, but none of them

Table IV *Physician s assessment response to betahistine Details for the symptom Vertigo*

Duration of therapy (weeks)	Vertigo (n = 8*)		
	Improved	Unchanged	Worse
2	1	5	1 (p = 0.50)
6	3	4	1 (p = 0.31)
10	6	2	0 (p = 0 02)
14	5	2	1 (p = 0 11)
20	6	2	0 (p = 0 02)
26	5	3	0 (p = 0 03)
40	6	1 (1)	0 (p = 0 02)
Final assessment 44–86	6	0 (1)	1 (p = 0.06)

experienced a return of his or her earlier condition

No other adverse effects of the medication were noted

Results of other observations

No marked changes were seen in blood pres sure in any of the patients during the study There was noted in most of the patients an *increase in the pinkness of the retinal macula* during the first few weeks of therapy but this is a subjective finding that is so difficult to quantitate that confirmation would need to be carried out in a more objective manner

DISCUSSION

A difficulty which arises in studies of the ef fect of a particular type of therapy in a condi tion like Ménière s Syndrome" lies in the selection of the method of control. These re sults show a clear improvement in the symp toms vertigo and tinnitus and also in the total symptom score for most of the patients during the trial

Such an effect might be falsely attributed to the therapy under test under the following circumstances

1) If at the time of inclusion into the trial the patients were in the midst of an unusually severe exacerbation or deterioration.

2) If the method of assessment or recording were changed during the course of the trial.

3) If the patient s judgement of the severity of his symptoms was altered during the course of the trial

4) If the treatment of follow up involved in the trial were associated with a marked and increasing placebo" effect.

5) If almost all of the patients happened to be selected at a time when their disease pro cess was "dying out"

Each of these possibilities has been con sidered. The date on which each patient was *included in the study was determined by the* date of his or her routine clinic attendance and the time of the year that the trial began was determined by the availability of the beta histine tablets All patients entered the trial between May and October 1968

Throughout the trial the method of record ing the results remained unchanged but some patients did not continue to keep daily re cords after 6 months. If this had influenced the physician s assessment of the symptoms obtained from questioning the patient then there might be expected to be a trend of change in the physician s record, which cor responded with the cessation of the main tenance of personal records by the patient. Such a trend was not seen

It could be suggested that participation in this trial and attention from a physician could

Table V *Physician s assessment response to betahistine Details for the symptom Tinnitus*

Duration of therapy (weeks)	Tinnitus (n = 9)		
	Improved	Unchanged	Worse
2	3	3	2 (p = 0 50)
6	4	3	2 (p = 0 34)
10	4	4	1 (p = 0.19)
14	5	3	1 (p = 0.11)
20	6		1 (p = 0 06)
26	4	3	2 (p = 0 34)
40	6	1	1 (p = 0 06)
Final assessment 44–86	6	-	0 (p = 0 02)

lead to either a decrease in the patients' own assessments of the severity of their symptoms or that the improvement seen was a prolonged placebo effect. It can be seen from the patient's total symptom charts however that throughout the study there occurred not only a progressive decrease in the severity of the symptoms, but also in the incidence of exacerbations. A placebo effect is most marked during the first few weeks of treatment when the patient is hopeful and perhaps enthusiastic about receiving a new or different form of treatment. In a disease such as this, which in these patients had shown itself to be incapacitating and progressive, an increasing placebo response would be remarkable.

The final possibility which must be considered is that at the time of entering the trial, in most of the patients the disease process happened to be at the stage of "dying out", that is the stage of the disease, where the severity and incidence of the episodes of vertigo, nausea and vomiting diminish and where the loss of hearing remains constant or increases gradually. The outcome of the condition is not reliably predictable, its duration is variable and the degree of damage which has occurred if or when progression apparently ceases is impossible to forecast, it is therefore not possible to make a judgement on the stage or future course in these patients on the basis of duration or severity of symptoms at the time of beginning the trial. However, 2 patients had kept records before the trial started, these did not suggest a progressive improvement in symptoms before treatment. It would be an unusual coincidence if the very patients selected for this study were not only in the phase of the disease where symptoms were decreasing, but were selected for inclusion at exactly that time when a noticeable decrease in the frequency of attacks and severity of their symptoms was about to occur. They were, in fact, included only because they were becoming progressively more incapacitated, and demonstrated no response to any of the treatments which were tried.

Table VI. *Physician's assessment, response to betahistine. For the symptoms Tinnitus and Vertigo at intervals throughout the study, total for all patients*

Duration of therapy (weeks)	Vertigo (n = 8)		Tinnitus (n = 9)	
Placebo	14	(10)	22	(19)
2	13	(11)	17	(14)
6	11½	(7½)	21	(17)
10	7½	(3½)	18½	(14½)
14	9	(5)	17½	(13½)
20	6	(2)	16½	(12½)
26	7½	(3½)	20	(16)
40	2½		14	
Final assessment (44–86)	½		10	
	$P<0.05$		P 0.05	
	(Spearman's test of rank correlation)			

It has been postulated that as a dilator of the microcirculation betahistine acts by improving the blood supply to an ischaemic inner ear (Elia, 1965 b; Godlowski, 1965).

Animal studies have demonstrated that stimulation of the sympathetic nerve supply to the inner ear gives rise to vasoconstriction and a reduction in the size of the cochlear microphonic potentials (Seymour & Toppan, 1951; Seymour, 1953, 1954).

Topical application of adrenaline to the stria vascularis of the guinea pig has demonstrated that intense spasm may occur which may last for several hours (Hunt & Fossbinder, 1947). In patients suffering an exacerbation of the symptoms of Ménière's disease, cervical sympathetic block may give rise to an immediate improvement in vertigo and a diminution in low tone hearing loss (Walter, Hunt & Fossbinder, 1941; Wilmot, 1957, 1960, 1961). In addition the reported beneficial effects of cervical sympathectomy and case reports on the benefits of vasodilators and histamine infusion (Wilmot, 1957, 1960, 1961, 1969) are in support of the concept that Ménière's Syndrome may be due to impaired blood flow to the inner ear. If this could be assumed to be proved then the activity of Serc could be attributed to its

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Duration of therapy (weeks)	Vertigo (n = 8)		
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6	3	4	1 (p = 0.31)
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DISCUSSION

A difficulty which arises in studies of the effect of a particular type of therapy in a condition like "Ménière's Syndrome" lies in the selection of the method of control. These results show a clear improvement in the symptoms vertigo and tinnitus and also in the total symptom score for most of the patients during the trial.

Such an effect might be falsely attributed to the therapy under test under the following circumstances:

1) If at the time of inclusion into the trial the patients were in the midst of an unusually severe exacerbation or deterioration.

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3) If the patient's judgement of the severity of his symptoms was altered during the course of the trial.

4) If the treatment of follow up involved in the trial were associated with a marked and increasing placebo effect

5) If almost all of the patients happened to be selected at a time when their disease process was "dying out"

Each of these possibilities has been considered. The date on which each patient was included in the study was determined by the date of his or her routine clinic attendance and the time of the year that the trial began was determined by the availability of the betahistine tablets. All patients entered the trial between May and October 1968

Throughout the trial the method of recording the results remained unchanged, but some patients did not continue to keep daily records after 6 months. If this had influenced the physician's assessment of the symptoms obtained from questioning the patient, then there might be expected to be a trend of change in the physician's record, which corresponded with the cessation of the maintenance of personal records by the patient. Such a trend was not seen

It could be suggested that participation in this trial and attention from a physician could

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14	5	3	1 (p 0 11)
20	6		1 (p 0 06)
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Table VII *Previous occupations and former and present status of patients Results of treatment*

	Previous Occupation	Former Status	Result of Treatment	Present Status
1 v d M	Housewife	Incapacitated	Failure	Found to have pontine angle tumour
2 Di	Housewife	Incapacitated	Success	Normal duties resumed
3 Em.	Nurse	Incapacitated	Success	Working half days
4 Co	Office worker	Incapacitated	Failure	Resumed previous occupation
5 v d W	Driver	Incapacitated	Failure	Without work
6. Spl.	Insurance agent	Incapacitated	Success	Normal work
7 Hu	Director of school	Incapacitated	Success	Work changed because of deafness
8 Bo.	Housewife	Incapacitated	Success	Normal duties resumed
9 An	Teacher	Incapacitated	Success	Normal duties resumed
10. Ja.	Church official	Incapacitated	Success	Normal duties resumed

microcirculation dilatory effect (Walter et al 1941 Hunt & Fossbinder 1942 Baez, 1968 1969 *Suga & Snow* 1968 1969)

SUMMARY AND CONCLUSIONS

Nine patients suffering from Ménière's Syndrome were treated with betahistine hydrochloride tablets for from 29 to 84 weeks continuously Daily symptom records were kept for at least 6 months in all patients and for longer in the majority At each outpatient visit the physician made a separate assessment of the patient's condition Audiograms performed before and during treatment were compared

The results showed that during the course of the study there was a progressive improvement in the symptom scores for vertigo and tinnitus. The trend of improvement was statistically significant. No clear adverse or beneficial effect on hearing could be seen from the audiograms Successful treatment with betahistine was accompanied by a marked improvement in the patients social activities

One patient who had previously suffered from asthma, had an exacerbation during the first 2 weeks of treatment with betahistine No other side-effects were reported.

The possible causes for the beneficial effects and the proposed mechanism of action of betahistine are briefly discussed

It is concluded that this progressive improvement in the symptoms tinnitus and vertigo in Ménière's disease is attributable to the treatment with betahistine.

ACKNOWLEDGEMENT

The author wishes to express his thanks for the help of Professor W F B. Brinkman and Dr C. I E. Jansen Department of Otorhinolaryngology Radboud University Hospital, Nijmegen

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HOW SHOULD A TREATMENT OF MÉNIÈRE'S SYNDROME BE EVALUATED?

Panel Discussion

Panel Chairman and Editor R. R. A. Coles

University of Southampton Southampton England

Chairman We have had many papers and much useful discussion today which have highlighted in different ways most of the problems concerned in any kind of therapeutic trial in Ménière's disease The biggest problem is the question of natural exacerbations and remissions, and the long period of follow up which is needed. This is five years according to McNally's recommendations, but we now have a suggestion that for a perfect trial, a much longer followup still is needed. This is one of many considerations on which we are forced into practical compromise as distinct from the ideal

One difficulty is in deciding what you regard as a cure and if you are going to talk about cures, a thing which has not yet been discussed in this symposium is whether the cases should be subdivided into early ones and long standing ones. In early cases it is relevant to consider the possible effects on hearing and tinnitus, also perhaps certain changes in sensitivity to caloric testing whereas in long-standing cases probably the hearing is already fairly bad and irreversibly so then, you cannot expect a return to anything like normal hearing but you may still achieve a "cure" because by this time the major complaint is vertigo which presumably arises from fluctuations in the resting tone of the affected vestibular organ and nerve Then there are the ethical problems associated with double-blind trials placebos, cross-over trials.

Finally or rather firstly there is the question of what criteria you are going to use to define the disease entity on which you are going to try to run a therapeutic trial. I think therefore that our panel discussion should commence with a discussion of the diagnostic features of Ménière's disease and Ménière's syndrome Should one include a wide variety of cases, or should the diagnostic criteria be strictly defined, or should the trial cover both diagnostic groups? Some have advocated fairly tight diagnostic schedules for Ménière's disease patients, together with a second more heterogeneous group termed Ménière-like syndrome or pseudo-Ménière's disease or some such name May I have some views on this, please?

Hinchcliffe Relevant to the Chairman's questions, there is the problem of whether or not such conditions as Lermoyez syndrome pseudo-Ménière's disorder and vestibular neuronitis are "formes frustes" or atypical forms of Ménière's disorder or whether they represent nosologically distinct disorders. There are now quantitative techniques, e.g. numerical taxonomy available which can indicate whether we are dealing with a homogeneous population or a heterogeneous one Our own application of these methods has shown that after we have excluded such acceptably distinct disorders as those due to toxins, trauma or organic disease of the nervous system, there re

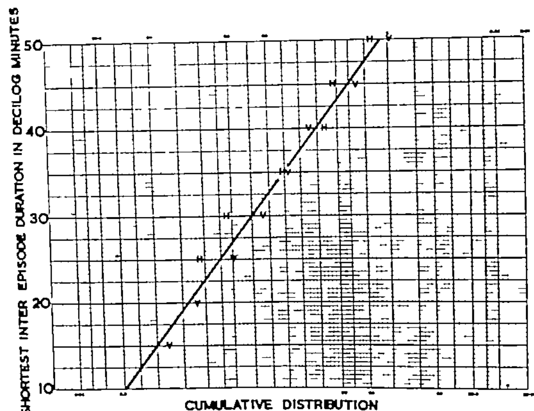


Fig 1 (Hinchcliff) *Cumulative distribution of shortest inter episode durations in Ménière disorder* (*V* vertigo, *H* headache)

mains a homogeneous population of vertiginous disorders In short, all other Ménière form disorders are most likely to represent Ménière s disorder in one form or another Thus, in the hypothetical study that we are considering today not only is it not necessary to exclude Ménière-form disorders other than the typical condition, but, since in overall medical practice they may be commoner than those showing the classical characteristics, it should be mandatory to include them.

In contrast to the concept of the homogeneity of Ménière s disorder—as a clinical condition—is the concept of a multifactorial aetiology Such a concept would help to reconcile, for example, the apparently conflicting assertions that the disorder is, on the one hand, an allergic one, and, on the other hand, a psychosomatic one. With respect to asthma, Kourilsky has reported that crises are always preceded by anxiety and that suppression of the emotional stimulus results in suppression also of the allergic manifestations.

Finally might I show some slides that demonstrate the distribution of some basic quantitative measures in the symptomatology of Ménière s disorder These measures could conceivably be of value in the assessment of therapeutic trials and in the comparison of the different series of cases reported by various authors so that we might ascertain how comparable these various samples are. Slide 1 shows the distribution of the shortest inter episode duration with respect not only to the

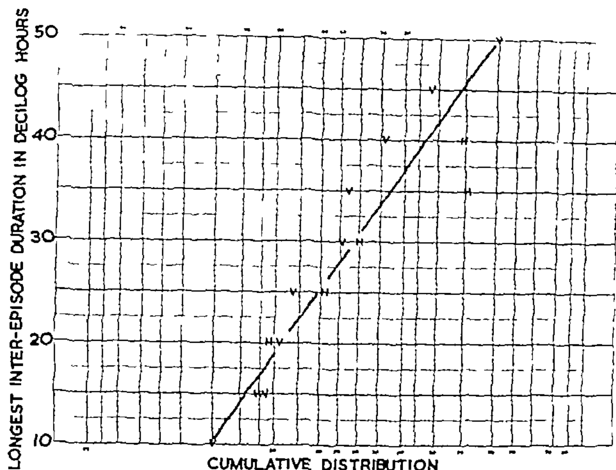


Fig 2 (Hinchcliffe) *Cumulative distribution of longest inter-episode durations in Ménière's disorder* (V = vertigo *H* = headache).

vertigo which affects patients with Ménière's disorder but also the headaches from which many of them also suffer The duration is expressed on a logarithmic scale It will be noted that not only do the shortest inter-episode durations of vertigo exhibit a straight line plot i.e a Gaussian distribution, but those with the headaches do also Moreover it is the same Gaussian distribution Slide 2 shows similar results for the longest inter-episode duration for both the vertigo and the headaches. The data indicate that in 2% of Ménière's patients, the longest inter-episode duration is more than ten years. Thus it can be argued that failure of a patient to have any more attacks in their lifetime is merely because the inter-episode duration has been extended to a period beyond their life span

Slides 3 & 4 show that there is a trading relationship between severity of the physiological deficit in Ménière's disorder and the personality aberration in these patients.

Chairman Any other contributors on this before I attempt to summarize upon that? No? Well we seem to be in complete agreement that one has to exclude other conditions very rigorously But what do we do with the remainder? One approach is to put them into two groups. (i) Those with the classic triad of symptoms, supported by appropriate signs yielded by the threshold audiometric, differential diagnostic, and vestibulometric tests that have been discussed in various papers. (ii) A second group in which the symptomatology is not quite classical such as cases which have not

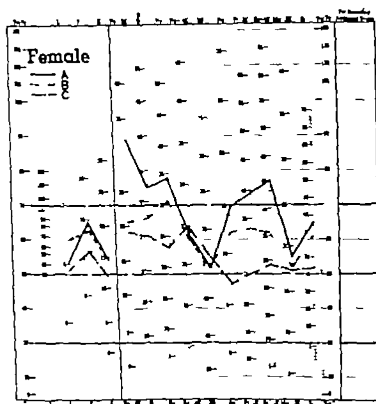


Fig. 3 (Hinchcliffe). *Relationships between hearing level and personality aberration in Ménière disorder. Group I (USA)* (*A* = median scores for subgroup with hearing level <30 dB (ASA 1951) at 500 Hz, *B* = HL 30-60 dB, *C* = HL >60 dB).

had tinnitus, or they have not had much deafness. One rather hesitates though to put in cases of deafness and tinnitus without vertigo. I think, Dr Hinchcliffe, that you would agree that episodic vertigo is the one symptom you cannot exclude although you may do without tinnitus or without deafness. Having classified the cases in two separate groups, you can either use both groups or, if you wish to restrict the size of the trial and obtain maximum precision, you can simply stick to as many classical cases of Ménière's syndrome as you can find.

The other approach, put forward by Dr Hinchcliffe, is simply to lump the material together and, if I understand him correctly, to do an analysis of the homogeneity of the group as a whole. I am not entirely clear how you

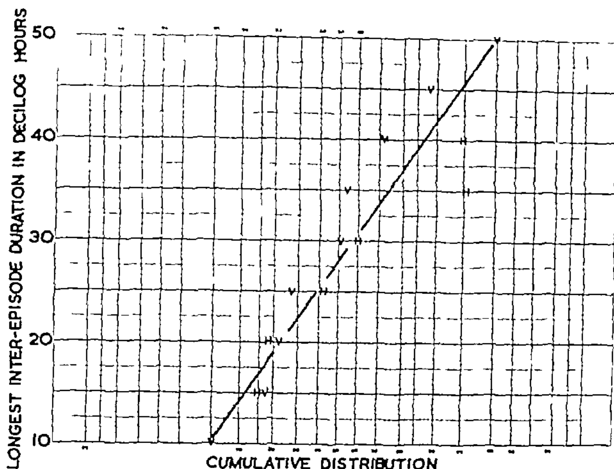


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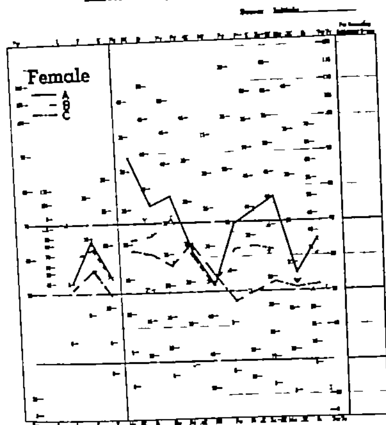


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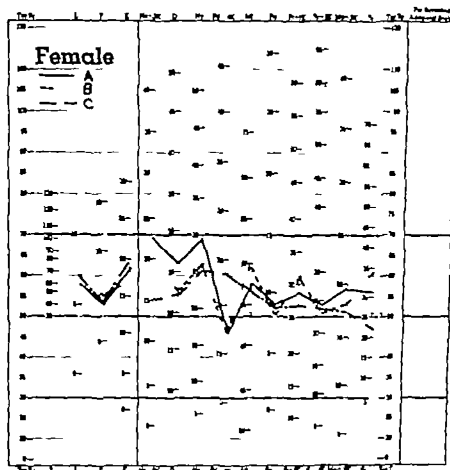


Fig 4 (Hinchcliffe) *Relationships between hearing level and personality aberration in Ménière's disord Group 2 (U.K.)* (*A* = median scores for subgroup with hearing level in poorer ear < 50 dB (BSI 1954) at 500 Hz, *B* = HL 50–60 dB *C* = HL > 60 dB)

proceed with that, but I'm afraid we cannot go into it in any more detail now

(*Question*) Could I ask Dr Hinchcliffe a question? There is a condition which has been recognized by Hallberg consisting of cochlear hydrops only: that is, hydrops of the cochlea without any hydrops of the utricle and saccule. And it is believed that many of these patients develop vertigo later In this specification when does the non-classical enter the classical phase?

Hinchcliffe I agree that difficulties always arise when one uses what medical people usually use i.e. a monothetic system of classifica

tion. According to this system a patient may be wrongly classified because of a failure to exhibit a crucial characteristic. For the purposes of our study I would agree that we must exclude any patient who does not suffer from vertigo. The clinical concept of Ménière's disorder is not identical with the histopathological concept of endolymphatic hydrops (Berggren, 1949; Wustrow & Borkowsky, 1960).

Chairman. Thank you. I do not think we have any particular difficulty there between the ideal and the practical compromise. It is a question of individual requirements and availability of facilities and time.

Wilmot. It seems to me that the biggest problem in differential diagnosis is not acoustic neuromas or head trauma or vestibular neuronitis, but the other vascular conditions which affect the head and neck, particularly the atherosclerotic group of patients. These are the people who present with vertigo, not necessarily of the classical Ménière-type, but who get giddy attacks; they often have bilateral hearing losses, which are not always equal. Sometimes, indeed quite commonly, they show evidence of recruitment and they often have good speech discrimination. Yet these people have not got Ménière's disease, although they may well have some endolymphatic hydrops as the result of a generalized disease process.

Now what we have been trying to do today, I think, is to sort out the effects of betahistine on the micro-circulation of the inner ear. But the greatest confusion in treatment is going to arise between people with a genuine micro-circulatory problem, which is probably psychosomatically induced, and a very much larger group of patients who are more often in older age groups and have pretty clear evidence of atherosclerosis which may be affecting the coronary arteries, the leg arteries, or the vertebrobasilar system. This is the group that really has got to be sorted out, and this is the group that we should know as much about as possible. I believe that the classical Ménière's syndrome has a different vestibular reaction than this group. Also the cases of head trauma and of vestibular neuronitis and so on.

The first thing we have got to do is to concentrate on the sort of testing which Dr Bertrand has been doing on a large scale and I have been doing on a smaller scale. This is in actually trying to measure vestibular function, because too much reliance upon audiometry and upon the caloric test have not really supplied the answer. What we have got to do is to see what difference in vestibular reactions we get in these different groups.

When you get a group of patients coming with vertigo, you have got to, as Professor Jongkees said this morning, examine the cervical spine and the cervical muscles. You have got to look for interstitial keratitis and you have got to do a thorough medical examination. You must spend time on these patients. But, *primarily*, you have got to exclude the effects of generalized atherosclerotic processes upon the inner ear.

Chairman. Thank you very much. I entirely agree. We have recently at Southampton been following up some of the work done by Litton & McCabe (1967) in the United States with their technique of "thermal vestibulometry". I know Dr Hinchcliffe, in London, has been doing likewise and I expect quite a number of other persons have too. In this, you do a series of cold caloric tests, gradually giving more and more cold stimuli until limited by the patient's discomfort. According to their paper, and supported by our own results and, I think, those of Dr Hinchcliffe too, this test seems to give a good differentiation between the *central* type of vestibular disorder and the peripheral one. Now I am not suggesting that this is the only technique for doing this. Mr Wilmot is recommending rotational vestibulometry. What I am quite sure of is that there is a lot more to be done in developing means of differential

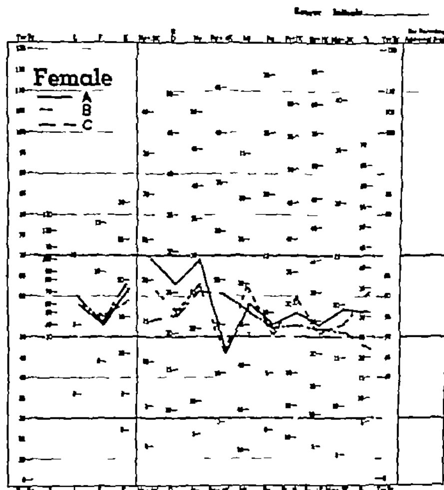


Fig. 4 (Hinchcliffe). *Relationships between hearing level and personality aberration in Ménière's disorder Group (U.K.)* (*A* = median scores for subgroup with hearing level in poorer ear < 50 dB (BSI 1954) at 500 Hz, *B* = HL 50–60 dB *C* = HL > 60 dB)

proceed with that, but I'm afraid we cannot go into it in any more detail now

(*Question*) Could I ask Dr Hinchcliffe a question? There is a condition which has been recognised by Hallberg consisting of cochlear hydrops only that is, hydrops of the cochlea without any hydrops of the utricle and saccule And it is believed that many of these patients develop vertigo later In this specification, when does the non-classical enter the classical phase?

Hinchcliffe I agree that difficulties always arise when one uses what medical people usually use, i.e. a monothetic system of classifica

ideal is surely to do every test that has been mentioned, but again we need a practical compromise. I think it would help therefore if we try to define what we regard as the minimum investigation. Would Mr Wilmot like to suggest what he would regard as the minimum investigation and then we can argue about what more must be added?

Wilmot It does seem to me that this is the crux of the whole thing. One must do pure tone threshold tests, by air and bone-conduction The simplest method of showing recruitment, in one or both ears, is to do a loudness discomfort level test, so that this could be your only test for pure-tone recruitment. The SISI test is not essential. Békésy audiometry is also essential to measure tone decay unless you are doing a special tone decay test. To recapitulate: air-conduction, bone-conduction, loudness discomfort level, Békésy fixed-frequency at 250, 1 000 and 4 000 Hertz, and a speech discrimination score. These are the essentials, provided you are quite certain that the deafness is purely neuro-sensory and that there is no conductive element If there is any doubt about this, then the acoustic impedance meter is also required

Hennebert I am afraid all the tests that Mr Wilmot describes are too time consuming I do not think that the bone-conduction tests must be done in every case with a tuning fork we can very well form an opinion about transmission Concerning tone decay my experience is that only 4 000 Hz is sufficient to demonstrate it It is far less frequent in the other frequencies

Chairman The minimum audiological requirement for patients who are going to take part in a therapeutic trial on Ménière's syndrome depends on the degree to which you are aiming to refine the diagnosis Personally I would like to see the sort of audiological work-up which has been described, but we can agree to differ in detail.

Hinchcliffe Could I de-emphasise audiological and vestibular measurements? One of the most valuable sources of diagnostic information, when we wish to ensure whether or not we are dealing with Ménière's disorder (especially vis-à-vis intermittent vertebro-basilar artery insufficiency), is the questionnaire, or anamnesis or history or whatever we wish to call it.

In the physical examination, a neurological examination covering at least the cranial nerves is necessary An examination for interstitial keratitis is mandatory in the ophthalmological examination

Frew I would also suggest that some radiological investigations, not necessarily of a complicated kind, should be added. At least, an X-ray of skull and an X-ray of the cervical spine. I noticed in Dr Hommes' paper that he did in some investigations a probably unnecessary lumbar puncture, together with radiology of the internal auditory meatuses and an internal carotid arteriograph. Surely the vertebral artery plays a bigger part than the internal carotid here. Basic radiology of the internal auditory meatuses is all that is needed unless one is going to do a full tomography and may be go on to contrast studies, which are not indicated at this stage. And as you know House and his co-workers found that something like 40% of acoustic neuromas when they are small have normal lumbar puncture protein.

Chairman. I think I want to get a consensus of opinion on whether radiological investigation should be an essential part. We'll consider it generally it might be X-ray of the internal auditory meatuses, it might be X-ray of the cervical spine, it might be arteriography or it might be all of these. Those who feel that radiological investigation is essential to the proper screening and investigation of patients to take part in a therapeutic trial in Ménière's syndrome, please show their hands? Fourteen. And those who feel it should not be? Two.

Lumbar puncture? Personally I would feel

diagnosis of vertigo using either or both thermal and rotational vestibulometric techniques

Bertrand I would like to comment briefly on the possibility of vestibular "recruitment" from rotational stimulation Vestibular "recruitment" has been defined by Litton & McCabe (1967) as "a response that is diminished near threshold building to greater increments of response as *one proceeds higher above threshold* by equal stimulus increments" They concluded that no vestibular recruitment" was observed in hair-cell lesions. It is to be noted however that the vestibular stimuli used consisted of *graduated caloric irrigations. Mr Wilmot s* recommendations of rotational vestibulometry certainly warrant further investigations. We have used routinely rotational stimulation with angular accelerations of 1 3 and 6 $/s^2$ and a sudden stop from 90 /s constant speed. In the normal ear the response using the speed of the slow phase as the parameter of analysis, is proportional to the stimulus used. Occasionally though, in the pathological ear from a marked hyporeflective response at the lower stimulations (1 and 3 $/s^2$ and even 6 $/s^2$) with the stronger stimulations of 6 $/s^2$ and a sudden stop from 90% the response frequently equalled that of the normal ear So that there seems to be a catching up" of the intensity of response obtained for the hyporeflective pathological ear with lower stimuli to that of the normal ear when stronger stimuli are used This could possibly be construed as "vestibular recruitment This phenomenon of "vestibular recruitment has been described by Greiner Contaux & Collard (1969) These authors claim that following torsion swing stimulations it is present in 5% of 2 000 analysed ENG recordings can be of a transitory nature and in 19% of the cases, when it is present, is related to a peripheral vestibular pathology This is compatible with our results.

Chairman I would like to ask you quite simply how do you stimulate the left ear only with the rotation test?

Bertrand It certainly must be agreed that rotational stimulation can and does, stimulate both ears. Nevertheless, physiological data seem to indicate that, for the horizontal semicircular canals, an *ampullopetal stimulation* evokes a stronger response than an ampullofugal stimulation An anticlockwise rotation would then elicit a response predominantly from the left labyrinth and vice versa for a *clockwise rotation*

Chairman I am afraid I would not agree but as Chairman I am *going to rule myself out of* order to argue it further

Wilmot Mr Chairman could we refer to left function and right function in terms of rotation test not left ear or right ear

Chairman Yes

Wilmot Can I just say something about recruitment in vestibular function because I would like to believe what Dr Bertrand said—that one gets recruitment in vestibular function the same as one does with auditory function in many cases of Ménière s syndrome—but this is not my experience In fact, I believe that one has the opposite finding in many cases of Ménière s syndrome. I find a remarkable lack of change of reaction in comparison to change in stimulus, and when you do exceed threshold, the reaction is much less than you would expect. So at the moment I am not in agreement with Dr Bertrand on this aspect of vestibular recruitment

Bertrand I am not saying at the present time that this catching up of vestibular response noted in certain cases is "vestibular recruitment" but only that this example may possibly be "vestibular recruitment"

Chairman I think we should now move on to the question of the pre treatment investigation From various papers, you have heard a whole host of tests that you could do The

that most people would feel that this is essential. I cannot conceive of it being left out. Would you agree? I am not suggesting that is the only vestibular function test. Does that dispose of the comments? Yes.

What additional tests? I would say positional nystagmus tests would have to be done and presumably investigation of any spontaneous nystagmus with electronystagmography (or electrooculography) and see what the effects of removal of visual fixation are. If they are abolished or reduced by darkness or eye closure, then it is probably a central disorder and not a peripheral one. This would seem to me an important differential diagnostic point. I suppose optokinetic nystagmus tests should also be performed, although I have always had difficulty in interpreting them. Is the general feeling that one should have the full vestibular investigation that is, positional, spontaneous, optokinetic and caloric tests? Yes.

Now we come to the rotation tests. Some feel that they have a great deal to offer. On the other hand there is one practical problem, a lot of people have not got the expensive and bulky equipment needed. Personally I feel that these tests should be optional only but this may be because I am biased by not being familiar with the technique and not having the equipment myself. Would someone like to present a case for rotation tests being essential to this investigation?

Wilmot. I think the crux of the question is getting the stimulus at the right level. The caloric test is a crude test. However you carry it out, it is still crude, and we should be concerned with very minor changes in vestibular function. All our emphasis in Ménière's disease for many years has been wrong. Our emphasis has been on the established disease after the reversible stage has been passed. It is only by changing our emphasis into interest in the early manifestations of vestibular disorders that we can ever really do anything to help our patients. The only time that this disease is really reversible is early. We must have equipment that shows us early changes of function. Not equipment comparable to dropping a brick on a man's toes and asking: Does that hurt?" He should be able to feel a feather and it is exactly the same in balance testing in that you need a development of the caloric test that gives the same fine degree of sensitivity which the rotation test gives. When this is possible I will take much more interest in the caloric test. I would say that anybody who is going to make any real progress in treating his patients has got to develop a method of fine vestibular stimulation.

Chairman. You would regard this as an essential feature for a trial of a drug or of any treatment? The terms of reference to this panel is how should a treatment of Ménière's syndrome be evaluated? Do you feel that this rotation test is an essential feature of the preliminary investigation?

Wilmot. Can I put it that anybody who can deliver fine vestibular stimuli with any equipment and can show repeatable results, then he should be allowed to investigate this condition. If he has not got equipment that will show this type of alteration, then I do not think he is in a position to evaluate a drug or a method of treatment.

Chairman. I am tempted, unless people disagree, to suggest that this should be an optional extra. If you have the facility to do it, use it by all means it will add to the value of the trial, but it is not an essential. Is there any disagreement on that? No.

Hennebert. I would just like to draw attention to another method of rotation evaluation. This is the alternate method, which we have used in the last few years and which is used in many centres in France and in Belgium. It is very easy. It is cheap, it is quite well normalized and standardized, and it is possible to reproduce the test results very well.

that this was not part of a routine investigation. It has quite a bit of morbidity attached to it in some hands at any rate, and it is unpleasant for the patient. Would those who feel that lumbar puncture should be a standard part of such an investigation please show their hands? None. Those who feel that it should not? Most think not. I am glad that you agree with me. Perhaps we can put it down as an optional extra. Let us now take the personality inventory which has been suggested by Dr Hinchcliffe. Would Dr Hinchcliffe like first to define what he means by this.

Hinchcliffe First, should the patient be examined by a psychiatrist and secondly should one use some quantitative measure of personality? That great English physician Ryle said "Measure the measurable and attempt to measure the immeasurable". There are lots of criticisms levelled at the MMPI (Minnesota Multiphasic Personality Inventory) but this measure is not only a quantitative one but correlations have been established between scores on its scales and various measures of auditory (see slides 3 & 4) and vestibular deficit in Ménière's disorder.

Chairman I want another show of hands please. By those who feel that a personality inventory is an essential part of the preliminary investigation? Three. By those who feel it should be an optional part which you can use if you are so inclined? Nearly everyone.

Are there any other essential investigations required?

Martinez I am not sure whether emphasis has been given during the neurological examination to examination of the gait with eyes closed and also the examination of the fundi of the eye by the otolaryngologist who is seeing the patient, that is, not necessarily requesting an ophthalmological consultation in all patients.

Wilmot Could we modify Dr Martinez' suggestion to clinical tests of balance?

Chairman Yes, you are saying that a good practice of otology should be able to encompass balance tests without having to bring in a neurological specialist, and ophthalmic examination without routine need for reference to an ophthalmologist.

Wilmot One does get a lot of information from simple tests, like standing on one leg, heel-toe walking, tiptoeing quickly, defence of equilibrium, and so on, and the whole of these tests can be run through in about one or one-and-a-half minutes. Another question though, is how are we going to exclude manifestations of atherosclerosis? These often appear later although with hindsight one might have suspected them at the first consultation.

Stuart I would suggest listening to the arteries in the lower part of the neck. You can often hear bruits. This is just one point; there are of course many points in the history also. The other thing I like to make a plea for is the 30-degree caloric test. If you do not get a response to a 30 degree caloric test, I think the patient should be investigated for an acoustic neuroma, especially the patient who is deaf. If you do not do this, you will miss the odd acoustic neuroma.

Chairman We should certainly include listening to the neck vessels as a particular test, but obviously general cardiovascular investigation, not least at any rate measurement of blood pressure and pulse rate, and rhythm, is needed. We shall come to calorics in a moment.

Martinez Still on the question of atherosclerosis, the fundus is very important and I would also rotate the neck and look for nystagmus which may arise if the arterial supply becomes shut off by the torsion of the neck. I would call cases like these vertebrobasilar insufficiency rather than Ménière's syndrome.

Chairman On vestibular function we have already mentioned caloric tests. I would imagine

You can still do your analysis of the whole group, but later if you have them sub-divided in this way you can, as you go along, collect more and more and eventually analyse each sub-division separately. I would go along with Dr Bertrand on this and say that we should have a definite method of grading along exactly the lines that he said.

Flynn. I also would agree with Dr Bertrand and Dr Wilmot but I would go a stage further especially if very small numbers are involved in a controlled trial, because if you have random allocation to one of two or more treatments, with small numbers you have a very good chance that you may not have comparable groups. You may run into trouble despite the fact that everything was double-blind. For instance, if you have ten patients in one group and ten patients in the other group in the first group you might have eight who are in the early and reversible stage of the disease and in the second group eight who are in a late stage of the disease. This is something that you cannot predict and something you cannot avoid, unless you select and categorize the patients before you allocate them to a form of treatment.

Chairman. And you have a different statistical plan for each of these sub-groups? You allocate them to a sub-group and then according to the sub-group you would give each patient either placebo or drug according to some prearranged plan?

Flynn. Yes.

Chairman. That seems to be a very sensible precaution.

Hinchcliffe. I would not agree that one should restrict the number of grades in one's assessment of severity to three. It would be better to use more grades of severity. It has been shown that, even if one wants to come out with three grades eventually more precision can be achieved by asking the observer to use a 9-point scale than collapsing results to give a 3-point scale.

Chairman. In any kind of experiment one ends up by adding, adding, adding to it. I recall how I used to battle with our statistician in deciding what number of subjects to plan for. She always seemed to double the number I thought of as enough, but I knew she was going to do that so I quartered the number I thought she would ask for and so on. Thus, experimental decision is so often a question of practical compromise.

Coming back now to our topic, I think the ideal is to have three groups, and a separate statistical plan for each of these groups. But is there any practical compromise that could be suggested here for smaller trials? Well, I think the answer is simply to take your patients, classify them, and present results for each class or grade separately. But unless you are going for a relatively large study I do not think you could follow your point, Dr Flynn, very easily because you would then need a minimum of say 30 patients or something of that sort. You would do that if you can, but only if your study is big enough.

We come now to the question of controls. This either involves placebo treatment, or the history of that *particular* patient before he was included *in the trial* and came under treatment, or simply a comparison with the known, if it be known, natural course of Ménière's disease aiming to show that the expected progress would be such and such and your treatment has modified it and made it something different. The first question then is whether you can compare treated results with the known history of Ménière's disease and use that as the control? My own feeling is that the course of Ménière's disease is too variable for this.

Hinchcliffe. No, Mr Chairman you may remember that I have presented data on the statistical distribution of the shortest, the long

Chairman Thank you very much. Is there any thing we have still missed out?

Hinchcliffe I would like to add serology and haematology In two consecutive series of one hundred patients, one case in each had leukaemia presenting as vertigo

Chairman Let us just ask for a show of hands. Serology and haematology Those who agree this should be done? Your point is well taken

I want now to direct the discussion to consider the minimum period of observation What I had in mind here is whether you can make up your mind on just one examination that the case is one of Ménière s disease and suitable for inclusion in the experimental series. Do you have to observe him for a period of time first? In some of these trials the patients were observed beforehand for long periods. May I have suggestions please, from those who this afternoon presented papers on therapeutic trials, as to what they regard as a minimum period of observation before including a particular patient in a trial.

Bertrand I would like to have these aspects taken into consideration first, whatever medical treatment is used, the patient is not considered cured but controlled. The second aspect is that I believe that a patient can be included in a study immediately after his first visit Finally that it must be considered very hazardous to give results relating only to three or even six or eight months of treatment.

Chairman We will be coming to your third point later What we must discuss now is beforehand. We have a suggestion here that once you have investigated the patient there is no need to wait any longer and observe him for a period of time Is there anyone who disagrees with that? No The next point is should you subdivide your patients into groups? The thing that I have in mind is this question of early and late cases. With the early cases you can perhaps look at all the facets of the treatment and the trial the effects on tinnitus, vertigo and deafness Whilst later on in the disease probably the vertigo is the only thing on which you may get useful results. Is it the general feeling that one should subdivide in this way or should you simply establish that each is a case of Ménière s disease in some particular stage and then lump all cases together?

Bertrand The patients which were included in my study were divided into three groups. The first group included the patients in the early stage of the disease in which, on at least one occasion there was a neuro-sensorial hearing loss which hearing loss can still revert back to normal hearing. Into the second group I classified those patients who in addition to the the symptomatology present between the vertiginous crises, had a permanent hearing loss or a permanent diminution of vestibular function Finally in a third group I have classified those cases who present severe vertiginous crises and are under consideration for surgery Statistically patients in Group I have a higher percentage of control than those of Group II and those of Group II higher than those of Group III. Patients presenting with Ménière s disease could probably be classified in more groups than three but it would be I believe, difficult to obtain an objective classification

Chairman. I think you have with your study which is a very large-scale one and long-term as well something approaching the ideal. When you have got such large numbers, then I think you should subdivide there is no doubt about that. But we may need a practical compromise for smaller trials. Is it essential to pick groups which are all early and reversible or all moderate or all severe? Or can you simply take 10 or 20 cases which may be somewhat heterogeneous with respect to stage or severity?

Wilmot Again I agree entirely with Dr Bertrand. I think we should have these three grades and that we should all think in these terms, even if we are collecting only a small number

You can still do your analysis of the whole group, but later if you have them sub-divided in this way you can, as you go along, collect more and more and eventually analyse each sub-division separately I would go along with Dr Bertrand on this and say that we should have a definite method of grading along exactly the lines that he said.

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Hinchcliffe No Mr Chairman you may remember that I have presented data on the statistical distribution of the shortest, the long-

est and the "average" episodes of not only the duration of vertigo but also of the intervals between episodes. These easily measured parameters could be used to show the effects of treatments whether we use the norms that *we have already established, or others.*

Chairman. So you feel it could be done It would be an acceptable way provided you explain what you have done

Hinchcliffe Yes!

Chairman And for that matter this would also go for any comparison with the patient's own history Now how about comparison with other therapeutic trials? I am thinking of the case where somebody else has published results with a different method of treatment, but using *the same criteria of diagnosis and the same* general format of trial. Say for example he had shown that 25% of the patients improved and the majority were not affected in your trial with another drug you find that 35% were improved. Can this be accepted as a valid comparison indicating that your drug is the better *one? Have we yet got to a stage of* definition of trials, particularly in Ménière's disease where you can do this sort of thing? My own feeling is that you have not. I think the variation between individual patients which have been selected for trials, however strict your criteria is so wide that you cannot compare your 35% success with somebody else's 25% If you get 95% and he gets 15% it is all right but fairly narrow comparisons of statistics are just not valid in this particular disorder I think the best you can hope for is to show that the thing is either ineffective slightly beneficial, moderately beneficial, or highly beneficial

Bertrand Certainly the comparison from one author to another is difficult and even hazardous in such a syndrome as Ménière's. However if the same author does a drug evaluation in a similar manner with two different drugs, he can compare the results obtained with either drug both for the clinical evaluation as for the objective tests. An example of this can be obtained from the results we obtained from the study with thiethylperazine *in which it was noted that the effect of this* medication produces a severe diminution of the vestibular response, as compared to the study done with betahistine HCl which demonstrated an increase of the vestibular response in the early stage of the treatment. Objective tests done on a patient, such as re*corded by ENG can be analyzed and compared* by the same author from one drug study to another or even from one laboratory to another if the same techniques and methods of analysis are used.

Chairman Obviously you can apply statistical *tests to the results of one trial compared with* another if the results are presented in the same format So subject to certain restrictions on sampling criteria it would seem useful and valid to compare one Ménière's syndrome drug with another even though tested in different trials with different patients.

Flynn I would like to say it depends on what it is that you are trying to prove when comparing the effects of one drug with another or with any other form of treatment. For example you can analyse the results from a trial which you have carried out yourself with one form of treatment and compare these results with those of another form of treatment, and convince yourself and many others that there is a difference between the two forms of treatment *But as Dr Hinchcliffe pointed out,* there is always going to be someone who will pick holes in it for a number of reasons. If we are trying to design a trial which proves or demonstrates without any doubt the efficacy of a treatment, then I think that to compare the results of one trial with another trial, which was done at a different time will always be open to criticism This also applies to any evaluation of the response to treatment if it is

compared only with the pre-treatment history of the patient.

Chairman. Coming to the question of double-blind trials, the thing that worries me is a doubt as to how blind they really are. I was not thinking so much of the experimenter's point of view but rather of the patient's point of view. I suspect that they can fairly quickly find out which drugs they are having or whether the drug has been changed. If it is a capsule, they only need to bite it on one occasion, or have a small leakage and there is a difference of taste or maybe they notice some side-effect or other effect from a particular drug. I would like to ask those who have carried out these trials what their experiences may have been? Do they really feel that the patients had no idea at all which drug they were taking, or that they were taking something different on some occasions?

Flynn. As you said, it depends on the side-effects of the drug. Usually, I think, the pharmacist who makes the placebo tablet tries to make it identical in as many ways as possible. One pharmaceutical company even claims that their placebos burn with the same coloured flame as the active tablets. But of course if you have a drug which has side-effects, then the patient can often distinguish a difference during two treatment periods. It is impossible or very difficult to find out if he does know or does not know. But the physician certainly should not know unless side-effects or clear therapeutic effects occur.

Bertrand. Double-blind study was started with betahistine HCl and it was impossible to determine at either the first or the second visit whether the subjects were receiving the drug or the placebo. This was not the case with the study with thiethylperazine. In that double-blind study, in which the patients were given either the drug or a placebo, the physician could determine by the questioning whether the subject was having the drug or a placebo, because of the frequency of side-effects which were present with that drug.

Chairman. In a double-blind trial, is it essential that the patient should not know that such a trial is going on and that there are two forms of tablet being given? Or should the patient be told? Should he be asked if he will participate in such a trial? This is really coming on to the ethics of drug trials, but I would like to take this point first.

Bertrand. I think that if the patient knows that he is on a double-blind trial, and that if he gets the active drug in the first part and he still gets one or two crises, he may start thinking "I am getting the placebo". Then, either he won't keep on taking it or you are introducing a psychological aspect. I think you are completely destroying the value of the double-blind technique in a disease such as Ménière's disease if the patient knows that he may be receiving a placebo. I do not think there is anything wrong with giving a placebo to a patient: the placebo-treatment in Ménière's disease exists in its own right and this is why I do not think it necessary to tell the patient.

Frew. In England this ethical standpoint has been a source of worry to many people for a long time, and only recently the Royal College of Physicians suggested that every hospital which engages in research should set up an ethical committee. We, at the present moment, are not allowed to carry out any form of trial without satisfying this committee that such a trial is not going to cause any damage to the patient.

Chairman. Does the committee insist on the patient being told, and asked if he would co-operate in the trial?

Frew. No. But I was referring to general principles of ethics.

est, and the "average" episodes of not only the duration of vertigo but also of the intervals between episodes. These easily measured parameters could be used to show the effects of treatments, whether we use the norms that we have already established or others.

Chairman So you feel it could be done It would be an acceptable way provided you explain what you have done

Hinchcliffe Yes!

Chairman And for that matter this would also go for any comparison with the patient s own history Now how about comparison with other therapeutic trials? I am thinking of the case where somebody else has published results with a different method of treatment, but using the same criteria of diagnosis and the same general format of trial Say for example, he had shown that 25% of the patients improved and the majority were not affected in your trial with another drug you find that 35 were improved Can this be accepted as a valid comparison indicating that your drug is the better one? Have we yet got to a stage of definition of trials, particularly in Ménière s disease where you can do this sort of thing? My own feeling is that you have not I think the variation between individual patients which have been selected for trials, however strict your criteria is so wide that you cannot compare your 35% success with somebody else s 25% If you get 95% and he gets 15% it is all right but fairly narrow comparisons of statistics are just not valid in this particular disorder I think the best you can hope for is to show that the thing is either ineffective slightly beneficial, moderately beneficial or highly beneficial

Bertrand Certainly the comparison from one author to another is difficult and even hazardous in such a syndrome as Ménière s. However if the same author does a drug evaluation in a similar manner with two different drugs, he can compare the results obtained with either drug both for the clinical evaluation as for the objective tests. An example of this can be obtained from the results we obtained from the study with thiethylperazine, in which it was noted that the effect of this medication produces a severe *diminution of* the vestibular response as compared to the study done with betahistine HCl which demonstrated an increase of the vestibular response in the early stage of the treatment. Objective tests done on a patient such as recorded by ENG can be analyzed and compared by the same author from one drug study to another or even from one laboratory to another if the same techniques and methods of analysis are used.

Chairman Obviously you can apply statistical tests to the results of one trial compared with another if the results are presented in the same format. So subject to certain restrictions on sampling criteria, it would seem useful and valid to compare one Ménière s syndrome drug with another even though tested in different trials with different patients.

Flynn I would like to say it depends on what it is that you are trying to prove when comparing the effects of one drug with another or with any other form of treatment For example, you can analyse the results from a trial which you have carried out yourself with one form of treatment and compare these results with those of another form of treatment, and convince yourself and many others that there is a difference between the two forms of treatment But as Dr Hinchcliffe pointed out, there is always going to be someone who will pick holes in it for a number of reasons. If we are trying to design a trial which proves or demonstrates without any doubt the efficacy of a treatment, then I think that to compare the results of one trial with another trial, which was done at a different time will always be open to criticism *This also applies to any* evaluation of the response to treatment if it is

is whether in Ménière's disease he should be told that at some stage he is going to have an inactive preparation or placebo.

Hinchcliffe. Could I perhaps suggest a way how we might resolve our dilemma? I think it was Bradford Hill who remarked "Whenever you do anything as regards treatment in medicine, if you do not do a controlled trial, then you really do an uncontrolled trial". So if we do not tell patients whenever we are doing an uncontrolled trial on them, which we do not, why should we tell them when we are doing a controlled trial?

Bertrand. I do not think that you should tell the patient that you are putting him on a double-blind study because of the psychological aspects to be considered in Ménière's disease and of the association of spontaneous remission which exists with this disease. However all of the patients are advised that they are on a drug trial evaluation and as already mentioned by Mr Frew such drug-trial evaluations in our hospital must be approved by a committee set up for such evaluation or such research. Therefore, we only advise our patient that he is on a trial medication, and we do not advise him that he will at one time or another receive a placebo especially when treating such pathology as Ménière's disease or Ménière's syndrome.

Chairman. I will try to summarize this although I am still in something of a dilemma, in spite of Dr Hinchcliffe's contribution. Tell the patient that he is taking part in a trial agreed. But do you tell him that he may at some time have a placebo or not? My personal feeling is that you need not, if you are quite convinced in your mind that you are not withholding something which would be of value to him. But I think there may be some people here who do not even hold with that. Am I going too far for you to agree?

Rounga. No, I can agree with your summary because you are speaking now about Ménière's disease or Ménière's syndrome and I must admit that to my knowledge there are no well-controlled studies at this moment indicating that some drug is effective in this disease. So, especially in this case I do not think that you really withhold from the patient anything. So you can tell him he is participating in a trial and indeed, in this case, compare an active drug with a placebo. But I must repeat the words of Dr Geuens again that it is very possible to compare the *new* treatment with an old treatment, the best so far in your hands.

Chairman. I would now like to consider the question of what period of observation is needed? Now I talked about cures earlier on, but we have had a very much better word suggested, in that we should be talking about control of the disease, not cure of it. Control over what length of period?

Bertrand. One patient in our series had, after three years of continuous vertiginous crises which completely incapacited him, a complete spontaneous remission for a period of 17 years. When evaluating the follow-up of a medical treatment for a Ménière's patient, when he asks the question "Will I get any more dizziness?" the only answer which can be given is that "The next crisis may come in a week, in a month, two months, five years from now or maybe never". I am *inclined* to compare this disease to something like diabetes. It is an easy thing to explain to a patient that diabetic patients are never cured, but may be controlled by various treatments. This is our objective, whether it may be a visit once a year to the doctor, talk to him, get a little psychotherapy or some medication, or an active treatment such as intravenous histamine. For practical purposes, however I think that we should take at least five years as the criterion: this would be a very good one but it is not a definite one as spontaneous remissions have occurred after periods longer than five years. Five year periods could be used in the same

Chairman On the general principle I quite agree Does anyone here feel that the patient has to be told? Or do you agree with Dr Bertrand that this is not necessary in fact that it would destroy the value of the trial if the patient does know that he is partaking in one?

Geuens I think it depends on whether the doctor himself believes that there exists an effective treatment If the doctor believes that there is an effective treatment, he should tell the patient that he is on a double blind trial, because in his mind he is withholding something from the patient So, when he believes that the drug is active he should not use a placebo but he could use another drug when one is available, that he thinks is next to or as active as the one he is studying

Chairman After what we heard in this morning s papers I do not think there need be anyone who need worry about this with Ménière s disease I do not think with the possible exception of Serc, that they are withholding anything which the patient should definitely be having and, if we are considering trials of Serc, that answers its own question.

In summary it is undesirable to tell the patient everything, unless for ethical reasons concerned with the fact that you may be withholding a treatment which you feel is likely to be beneficial under these circumstances, you *should tell him Is that summarised all* right? Yes.

We come now to the form of therapeutic trial and the ethical standpoints. Quite a lot of lively arguments came up during the tea interval as to a practical compromise here Whether you can or cannot use placebos, and what the form of the trial should be

Menon I agree with Dr Bertrand that in Ménière s disease there is no necessity really to tell the patient that he is on a double-blind trial. On the other hand, it is quite another problem, which I *think should be brought* forward, whether one should use placebo to compare with the drug being evaluated or whether the evaluation must always be with another allegedly active drug I think there must be different points of view as to whether the placebo should be used or not. And I would like to hear some other opinions on this.

Rosinga. I think we must realize that when you do a trial with drugs which may or may not be effective you are doing experiments in man After the Nürnberg-trial and the Declaration of Helsinki I think that in principle it is only ethical to tell the patient that he is participating in a trial When you do not I think you are not in agreement with the Declaration of *Helsinki* But of course there are sometimes difficulties that may arise from this policy and therefore I can only speak of the principle It is our policy as a matter of fact *in this company to instruct the investigator* to tell the patients that they are participating in a trial. I think that is really the only way you should do it

Chairman. It is a question, if you are the physician in charge of examining your own conscience on whether to withhold a drug or not But if having examined your conscience in all honesty you feel that you are not hazarding the patient, his health his general wellbeing or anything else, by conducting a particular form of trial, then I would have *though that in spite of the Nürnberg-trials and* the Declaration that followed, your conduct was correct. It is a question of giving positive thought to and following the dictates of your own conscience.

Menon I entirely agree with Dr Rosinga The question here is not whether the patient is informed that he is participating in a trial, but whether he should be told that he is going to have a placebo at some stage of the trial. Of course every patient I believe must be informed that he is participating in a trial in*volving the evaluation of drugs.* I am sure most patients realise this anyway The question

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manner as a five year cure in cancer is used which does not mean that a patient does not have any more cancer because he has survived five years since the original diagnosis of that pathology

Chairman. Of course with cancer it is a question of follow up after some relatively short period of treatment. But with Ménière's disease it presumably is a question of continued treatment Do I understand that you would like to have the patients on this drug or that regime for a period of five years, and then compare their symptomatology and objective signs at the end of that period with those at the start of treatment or with the otherwise expected progression of the disease?

Bertrand. At the present time if there is control after one or two years of medication I will stop the medication but, should the vertiginous crises reappear I would ask the patient to start taking the medication again and consult his referring physician In any case since this is a disease which can recur I always make it a point that they should have a review at yearly intervals for a few years.

Chairman At this point I think we need some clarification on our discussions. If one is really looking for the controlling effect of a treatment surely you can look over quite a short period of time? If you are looking for a "cure then you need this long follow up period to be sure that there has been a "cure" or reasonably sure that there has been a cure" in the majority of patients, anyhow Of course many of the surgical treatments of Ménière's disease are aimed at long term results. It is hoped that one operation will settle the patient for many years, if not permanently Perhaps this question of five year observation really refers to the one-off surgical type of treatment rather than drug treatment aimed to control If you feel that the drug treatment is going to do something perhaps by improving the microcirculation to permanently correct something that was wrong, then obviously you have got to do a long-term follow-up to see if this temporary improvement is maintained or not. But I do not think anyone here has that idea with respect to treatment with for example, Serc or with any other drug It is not going to produce a permanent cure but it may control the symptoms at the time of administration If they recur then presumably you give the drug again

Wilmot Dr Bertrand and I have shown that there is an effect upon vestibular function of giving this drug Now it would be nice to know certain specific things about this. First, what is the minimum dosage with which we could produce this improvement. Secondly how long does this objective change in vestibular function last after the cessation of treatment. These are relatively short term goals, which could be found out quite soon There are a lot of studies like this which would help because the aim as you just emphasized, is not to keep people on treatment for the rest of their lives, but to know how often to treat them and how long the effect of the drug is likely to act after the treatment is stopped. Dr Bertrand's study in depth or at length should give us further information on this, but we can also do these short term studies.

Hinchcliffe Is it not now appropriate to discuss what form of therapeutic trial should be undertaken? I would not accept that Ménière's disorder is such a peculiar disorder that it is impossible to subject it to a double-blind cross-over trial. I would also add that there are types of therapeutic trials, e g. sequential analysis, where it is possible to stop the trial as soon as the point is reached where it could be known that one method of treatment is superior to another

Could I also mention at this point very briefly my own practical experiences when I started double-blind trials in Ménière's disorder some years ago? When patients returned for follow-up, I might ask "Well how are you?"

I am fine. In fact I was able to stop the drug after two days" Or else the patient would say "Oh, by the way it was alright for me to carry on taking the drugs that my own doctor gave me wasn t it?" It was indeed exasperating.

Finally might I ask two questions. First, should we throw out the placebo-responders? And secondly should we use an indicator e g. a substance in the drugs that would be detectable in the urine, which would confirm that the patient had indeed taken the drugs?

Chairman. I think we should add that to the list of optional extras. It would be good if you could do them, but perhaps it is not absolutely essential.

Hinchcliffe An initial placebo-responder trial should be considered very seriously in planning this programme.

Flynn This problem is not restricted to trials in Menière s disease only but to any clinical trials. Only yesterday I came across such a study not in patients with Ménière s disease, in which more than 100 patients were followed. They were given a medicine containing an indicator and urine samples were collected during several months of follow-up they were also asked to bring back the bottles with any remaining medicine in them Of course some patients get up to all sorts of tricks, once they suspect that you are counting how many tablets are coming back They calculate how many they should have taken and then throw these away And it is also possible that intelligent patients can guess that you want a urine sample in order to check whether he has taken the treatment But what was outstanding from the study was that only in ten patients was there disagreement between the urinary results and the results from counting the returned bottles with contents Of course this was not in Ménière's disease, and maybe Ménière s patients respond in a different way

Chairman. Thank you for stressing the importance of these features in the design of the therapeutical trial. You are supporting Dr Hinchcliffe s views and also his suggestion of having an initial trial for the placebo responders. Anyone disagree? No

There is also the possibility of doing double-blind parallel experiments, as distinct from the double-blind cross-over ones. If you find a cross-over is difficult you could perhaps do the trial in parallel, half the subjects having one treatment and half the subjects the other and then compare the two groups. Would that be acceptable?

Bertrand. Well, it would take too long to discuss that.

Chairman Yes, we are short of time now May I then raise very briefly the question of a let-out clause mentioned earlier this afternoon. How would you bring that into the format of a trial?

Flynn. The let-out clause was mentioned in connection with a further study by Dr Hommes. He could not agree to do a double-blind trial, originally with betahistine in Ménière s disease, because the patients were completely incapacitated and, although there had been failure of all treatments which had been applied, as has been stated today there are so many different types of treatment which he could have tried that it was not justifiable to treat them with placebo When it was discovered that almost all of the patients responded, it was thought that there was one way in which it could be confirmed whether this was or was not a real drug effect. And this was to stop the treatment in half of the patients, but without informing them that there had been a change in their therapy If you once informed them, they would immediately I am sure, have some kind of a relapse in their symptoms. But if the patients in the placebo group, not knowing the nature of the tablets, very rapidly develop a relapse of

symptoms but the patients in the betahistine group do not, this will permit one to immediately commence active treatment again in those relapses. In addition this permits one to observe whether or not treatment needs to be continued at the same time eliminating the psychological effect of stopping or changing the treatment

Chairman So the let-out clause would be for the experimenter to know about the change of treatment and to be free to adapt accordingly The patient would not be given any explanation of this?

Flynn No

Chairman Good, that was the point I wanted to cover I think we have covered most of the agenda for this discussion The post-treatment investigation I feel is simply a replica or near replica of the pre treatment investigation. As to the criteria of success or failure I do not think this is really relevant to this discussion. It would take too long anyway and it has been covered pretty well in the papers which have listed the tests and various investigations performed That concludes the panel discussion

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SUMMARY OF PANEL DISCUSSION

(prepared, retrospectively by the Chairman)

The full text of the panel discussion on "How should a treatment of Ménière's syndrome be evaluated?" is given on the preceding pages, but it may help the reader who is contemplating carrying out a therapeutic trial in patients with this disorder to refer to the summary which follows.

Diagnosis of Ménière's disorder to be utilised in the patients

1 Classical triad of symptoms should be complete if possible but vertigo is the key symptom.
2. Homogeneity established statistically
3 A detailed medical history with (optionally) a personality inventory
4 A full neurological and cardiovascular examination with special emphasis on the cranial nerves, optic fundi gait and balance B P and pulse neck vessels, with (optionally) lumbar puncture
5 Audiological investigation by tuning fork tests, pure-tone a/c and b/c audiometry Békésy audiometry or tone decay tests, a recruitment test, and (preferably) speech audiometry
6 Vestibular investigation spontaneous nystagmus positional nystagmus, neck torsion nystagmus, caloric tests or rotation tests, (optionally) thermal vestibulometry
7 Radiology of skull (petrous bones) and cervical spine
8 Haematology (haemoglobin and cell count) and serology (W R. et al)

Classification of patients (into 3 stages)

1st stage early type remissions(= reversible) analyse for a variety of symptoms,

e.g. deafness, tinnitus, vertigo, headache.

2nd stage- persistent hearing loss, slight vestibular hypofunction.

3rd stage- advanced hearing loss and vestibular hypofunction analyse for control of vertigo.

Form of therapeutic trial

Double-blind trial with placebo or another active drug cross-over or parallel.

Preferably an initial trial for placebo-responders.

Inform the patient that he is on a drug trial, but not that there is a placebo. Placebos justifiable if (i) you are sure you are not withholding a treatment of value to him and (ii) a let-out clause by which the experimenter can modify the treatment if the placebo causes a serious relapse

Short periods of treatment and placebo to determine the immediate controlling effects of the drug, or a long-term study with follow up over many years to ascertain the "five year cure" rate.

Analysis principally by frequency and severity of vertiginous attacks, also by audiometric and vestibulometric changes, and by other symptoms.

Acta

OTO-LARYNGOLOGICA

SUPPLEMENT 306

Vestibular Disturbances in Clinical Otosclerosis

BY

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I Introduction

Otosclerosis is one of the most carefully studied diseases of the ear. Hearing loss caused by what is now called stapedial ankylosis was described by Valsalva as early as 1735.

So far the etiology of otosclerosis has remained obscure in spite of the numerous theories suggested. Delayed physiological development, inflammatory processes, cartilaginous deposits in the region of the fissula ante fenestram, disturbances in the blood supply, mechanical stimuli, etc. have been described as possible causes of otosclerosis. It is obvious that there are constitutional, local and activating factors which are responsible for the development of otosclerotic foci either individually or jointly (Altman, 1962).

For the last few years the fundamental study of otosclerosis has principally been devoted to the histochemistry of otosclerotic foci. A significant elevation in the activity of alkaline phosphatase and, on the other hand, an equally significant fall in the activity of lacticacid dehydrogenase have been revealed. Some changes have also been shown in the matrix of the otosclerotic bone, for instance in the number and construction of the polysaccharides.

In addition to typical conductive hearing loss, patients suffering from otosclerosis also often have perceptive hearing loss. Cochlear lesions are considered to be due to secretions from the active otosclerotic foci which have found their way into the endolymph (Shambaugh, 1959).

Vestibular disturbances even appear in patients suffering from otosclerosis (Fisch, 1965). These may be derived from otosclerotic vascular changes due to the disease or from biochemical changes in the inner ear fluids.

Because the hearing loss in otosclerosis is dominant, otosclerotic patients have not been examined for other disorders associated with otosclerosis as carefully as for hearing. Unsteadiness in walking and stopping can, however frequently be observed in these patients. In electronystagmographic investigations, findings, obviously differing from the normal, have been revealed (Meurman et al., 1969). It is obvious that further studies of these changes will throw additional light on the general view of otosclerosis.

I Introduction

Otosclerosis is one of the most carefully studied diseases of the ear Hearing loss caused by what is now called stapedial ankylosis was described by Valsalva as early as 1735

So far the etiology of otosclerosis has remained obscure in spite of the numerous theories suggested Delayed physiological development, inflammatory processes, cartilaginous deposits in the region of the fissula ante fenestram, disturbances in the blood supply mechanical stimuli, etc. have been described as possible causes of otosclerosis It is obvious that there are constitutional, local and activating factors which are responsible for the development of otosclerotic foci either individually or jointly (Altman, 1962)

For the last few years the fundamental study of otosclerosis has principally been devoted to the histochemistry of otosclerotic foci A significant elevation in the activity of alkaline phosphatase and, on the other hand, an equally significant fall in the activity of lacticacid dehydrogenase have been revealed Some changes have also been shown in the matrix of the otosclerotic bone, for instance in the number and construction of the polysaccharides.

In addition to typical conductive hearing loss, patients suffering from otosclerosis also often have perceptive hearing loss. Cochlear lesions are considered to be due to secretions from the active otosclerotic foci which have found their way into the endolymph (Shambaugh, 1959)

Vestibular disturbances even appear in patients suffering from otosclerosis (Finch, 1965) These may be derived from otosclerotic vascular changes due to the disease or from biochemical changes in the inner ear fluids

Because the hearing loss in otosclerosis is dominant, otosclerotic patients have not been examined for other disorders associated with otosclerosis as carefully as for hearing Unsteadiness in walking and stopping can, however frequently be observed in these patients. In electronystagmographic investigations, findings, obviously differing from the normal, have been revealed (Meurman et al., 1969) It is obvious that further studies of these changes will throw additional light on the general view of otosclerosis.

II The aim of the study

The aim of this investigation was to clarify the vestibular disturbances in patients suffering from otosclerosis. The following main points were studied

1. Does positional nystagmus occur in these patients?
2. Do the findings of caloric tests differ from the normal reactions?
3. Is there any possible correlation between hearing impairment and electronystagmographic findings?
4. What is the threshold of angular acceleration and deceleration in these patients, and does the threshold deviate from the normal values?
5. Do the findings of post rotatory nystagmus differ from the normal results?

III Review of the literature

A. Occurrence of otosclerotic foci

The importance of distinguishing between clinical and histological otosclerosis must be emphasized in any comment on the incidence of otosclerosis Engstrom (1940) revealed histological otosclerosis on the temporal bones in 12 per cent of 200 autopsies On the other hand Guild (1944) demonstrated histological otosclerosis in only 8,3 per cent of 518 whites and 1 per cent of 482 negroes Clinical otosclerosis, on the other hand, can be found in about 1 per cent of the white population.

Otosclerosis usually involves both ears Yet the frequency of histologically unilateral otosclerosis in the series of unselected subjects has been established at as high as 30 per cent by Guild (1944) 25 per cent by Nylén 1949) 13 per cent by Cawthorne (1955) and 15 per cent by Larsson (1960)

The size of the otosclerotic foci observed in autopsies varies greatly from a microfocus, demonstrable only in the electron microscope to very large focus, replacing most of the labyrinthine capsule (Guild, 1944 Nylén, 1949 Beikert, 1965 Chevance et al 1969) The area of the labyrinthine capsule immediately in front of the oval window is known as the site of predilection of the otosclerotic focus The borders of the round window are also frequent sites for otosclerotic foci. A primary focus may however occur even in the stapes footplate, around the cochlea, near the internal auditory canal, or less often around the semicircular canals

The focus nearly always originates in the endochondral layer of the labyrinthine capsule extending in many cases into the periosteal layers as far as the mucose of the tympanic cavity and into the endostal layer of the endosteum of the labyrinth Protrusions into the tympanic cavity in the form of exostoses are frequent Less common are encroachments upon the lumen of the labyrinth Where the focus reaches the mucoperiosteum of the tympanum and the endosteum of the labyrinth, these show varying degrees of fibrous thickening and increased vascularity (Shambaugh, 1959)

Examinations of 2 086 operated ears revealed that cochlear nerve involvement is present twice as often when otosclerotic foci are situated in the horizontal semicircular canal, compared with the frequency of the involvement when the canal is not affected (Seligman and Shambaugh, 1951) Histological otosclerosis is at any rate quite frequently asymptomatic. Most otosclerotic areas do not cause ankylosis of the stapes, even if located at the anterior margin of the oval window

In one patient suffering from the symptoms of Ménières disease the lateral semicircular canal was found at autopsy to be full of otosclerotic bone (Bretlau and Jorgensen, 1968)

B. Histological picture of otosclerosis

Otosclerosis is a disease of the bony labyrinthine capsule, frequently developing in areas where embryonic cartilage persists The pathological process is characterized by resorption of the normal bone, often around the blood vessels, and by the replacement of normal bone with cellular fibrous connective tissue. Areas undergoing active resorption are extensively vascularized

Wolf and Bellucci (1960) have suggested that some enzyme serves as the initiating factor of decalcification. Chevance et al (1961) suggested that the focus shows alkaline phosphatase during the first phase and the whole of the second phase until the bone is completely calcified. Alkaline phosphatase will then disappear The enzyme was extracellular except in osteoblasts where it was found to be intracellular Ricci (1962) observed that the activity of alkaline phosphatase increases in the focus He discovered

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alkaline phosphatase in both the osteocytes and the ground substance Abnormal accumulation of mucopolysaccharides in the otosclerotic focus was also observed Ricci suggested that the primary cause of otosclerosis was a certain change in the ground substance. Alberti and Tarkkanen (1963) have shown that there is an increased amount of leucine aminopeptidase and non-specific esterases present in the otosclerotic lesions, particularly in the perivascular fibroblasts and the osteocytes.

The participation of vascular changes in the genesis of decalcification has also been proposed (Wolf and Lempert 1965) Ruedi (1964 1969) observed abnormal vascular connections between the membranous labyrinth and the focus. These take the form of a circumscribed increase in the vascular loops and a proliferation of the epithelium of the stria. It appears that this strial proliferation probably occurs as a result of a circulatory disturbance in the region of the cochlear branch of the internal auditory artery The circulatory disturbance is caused by vascular demands made by the actively growing otosclerotic deposit.

It has also been verified that there are microfoci between the focus and normal tissue demonstrable only under an electron microscope (Chevance et al. 1969) The endothelial cells of the capillary network of the focus were however found to be normal

C. Changes in the composition of the perilymph in association with otosclerosis

The nature of the origin of the perilymph has not yet been clarified The perilymph is assumed to be of an extracellular character with low potassium and high sodium concentration.

In 122 otosclerotic patients the perilymph and the serum showed the same frequency dispersion for the concentration of glucose, calcium, sodium, and potassium. The values of maximum lacticacid dehydrogenase activity in the serum and the perilymph did not differ The values were much higher in the serum and the perilymph than in the liquor The mean phosphate concentration of the perilymph was also higher than that in the serum (Schindler et al. 1965) In 15 patients suffering from severe otosclerosis the contents of the alfa and beta globuline fractions had reduced (Chládek and Opplt 1966) The latter established further that there was a distinct relationship between the range of the protein spectrum in the perilymph and the activity of otosclerosis (1968) A correlation between the increased potassium and protein values and the preoperative hearing impairment for the bone conduction at 4 000 Hz was statistically proved by 155 otosclerotic patients (Rüedi, 1965) No statistical correlation was, however evident between the increased potassium and protein values and the pre- or postoperative vestibular symptoms in otosclerotic patients. Alkaline phosphatase was also found in the perilymph of otosclerotic patients. The mean value was as high as 2,3 B.E. (Bodansky Einheiten = Bodansky Units) There is no alkaline phosphatase in the perilymph of a normal ear

D Vertigo and electronystagmographic findings in patients suffering from otosclerosis

a. Electronystagmography (ENG) and caloric tests

Studies of vestibular changes in otosclerotic patients are remarkably less frequent than those of other otosclerotic disorders. Before the ENG-era, disturbances in the vestibular system could only be verified in extremely few otosclerosis cases. Although 27 per cent of 77 patients declared anamnestically that they suffered from vertigo only five cases revealed deviations from the normal reactions in the caloric tests (Rasmussen, 1949) Likewise Hulk and Jongkees (1950) were unable to verify either spontaneous or positional nystagmus, on the one hand or deviations in the caloric tests on the other hand, when studying 50 patients, 30 per cent of whom declared anamnestically that they suffered from unsteadiness while walking and from fits of dizziness on stopping

Aschan et al. (1956) were also unable to verify any nystagmus in a clinical investigation with Frenzel's glasses on one patient who showed spontaneous nystagmus in the ENG recording Reinecken (1960) described some electronystagmographic findings in as

many as 25 per cent of patients suffering from clinical otosclerosis before operation. Fisch (1965) manifested spontaneous nystagmus in eight and direction-determined positional nystagmus in seven cases of a total number of 52 patients, i.e. jointly 28,8 per cent of cases

Meurman et al (1969) found approximately the same percentage of nystagmus, but in the total 110 otosclerotic cases studied by them, there were only two cases with direction-changing positional nystagmus while the figure for direction-determined nystagmus was as high as 22 Twenty-three subjects in the same study of patients showed abnormalities in the caloric tests

In eight patients the caloric excitability was found to be reduced in the poorer ear while six subjects revealed reduced caloric excitability in the better ear Directional preponderance to the side of the worse ear was observed in six cases, while there were three cases with directional preponderance to the side of the better ear

b Rotatory tests

Since Barany's first introduction (1907) of rotatory tests, his original method has sustained several modifications When the rotating chair was employed in the earliest period of the method, it was the sensation of turning during and after rotation that was calculated in the first place The postrotatory nystagmus was also computed The modern rotating chair enables us to produce very delicate and minute accelerations and decelerations ENG too makes it possible to record most subtle divergences in nystagmus This in turn permits more physiological irritation of the semicircular canals than before As well as calculations of postrotatory nystagmus, computations of the thresholds of nystagmus made feasible by the modern rotating chair

As early as 1875 Mach showed by torsion of two suspended wires that the threshold for sensation of acceleration varied between 2 and 3 /sec² A more recent investigation indicates that the minimum perceptible acceleration when applying small accelerations of prolonged activity by means of torsion swing is as low as 0,5 /sec² (van Egmond, Groen and Jongkees, 1949)

In the tests executed by employing the rotating chair Hilding (1953) de Vries and Schlerbeek (1953) and Roggeveen and Nijhoff (1956) showed that the threshold of minimum perceptible acceleration and deceleration varies from 0,25 /sec² to 3,5 /sec²

By utilizing an ENG recording of per rotatory nystagmus Montandon and Russbach (1956) have shown that the threshold of nystagmus and the sensation of turning is approximately 0,8 /sec² in normal subjects, and this value applies to acceleration and deceleration Decher (1965) however obtained somewhat lower threshold values, approximating 0 4 /sec²

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In patients suffering from otosclerosis, the threshold of sensing turning is raised (Hulk and Jongkees, 1948) Postrotatory nystagmus has been established as being of shorter duration in otosclerotic patients than in normal subjects (Rasmussen 1949) On the other hand, Pursiainen has measured about the same duration of postrotatory nystagmus in otosclerotic patients as in normal subjects (1954) while the threshold of after-nystagmus in otosclerotic patients is raised (Hulk and Jongkees, 1948)

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In supine position
In both lateral positions and
with head hanging

The nystagmus findings were considered positive if the speed of the slow phase of the horizontal nystagmus exceeded 7°/sec.

The optokinetic nystagmus of the subjects was investigated at 30 and 60 /sec to the right and t the left alternately to exclude ertigo other than labyrinthine.

b Caloric tests

The caloric tests were performed according to Hallpike with the following exceptions The irrigation time was only 30 seconds The induced nystagmus was recorded for 70 seconds while the subject kept his eyes closed Thus reaching the culmination phase was positively secured At the 70th second the subject was requested to open his eyes and to fix his gaze on a fixation light which was located approximately two metres directly in front of the subject For each irrigation total amplitude and the angular locity of the slow nystagmic phase during the culmination phase were calculated The result was considered canal paresis (unilateral hypoexcitability) when reactions before the fixation in one ear were 20 per cent weaker than those in the other ear Correspondingly the result was regarded as directional preponderance when the intensity of nystagmus with a tendency in one direction was 20 per cent greater than in the ther All the subjects whose ocular fixation index (OFI) was higher than 50 per cent were excluded because these subjects the origin of the nystagmus observed in ENG investigation might be other than labyrinthine (Demanez and Ledoux, 1970)

Silver silverchloride electrodes 7 mm in diameter were employed The tw recording electrodes were located on the skin near the temporal canthi of the lids of the two eyes, the earthed electrode was placed on the skin of the forehead The electrodes were fixed with adhesiv tape and electrode jelly was tilized to improve the contact DC differential amplifier direct ink writing (Elema mingograph) was employed Before and after every investigation the apparatus was calibrated by a ten degree movement of the eyes.

c. Rotatory tests

The rotatory tests were carried out by means of Polman's rotating chair (Polman Mod. 11 e 111) which enables linear adjustment of acceleration and deceleration speeds from 0,2 /sec² onwards. The same type of electrode and the same pattern of fixating the electrodes were used as previously An A C condenser coupled amplifier (Polman Mod MP 11) time constant 2 seconds, was utilized for the recording. All recordings were performed in darkness The subject's head was fixed tilted 30 degrees forward from the vertical.

The linearity of acceleration and deceleration of the chair was controlled by the following method All the possible acceleration and deceleration speeds employed were investigated by accelerating and decelerating the chair for exactly 30 60 and 90 seconds. After this the rotating time of the chair was measured as the mean time f 10 rotations. The speed thus obtained was the same as the theoretical speed ± 5 per cent Thus the linearity of acceleration and deceleration was confirmed.

The threshold of acceleration and deceleration was measured in the way described below The subject was accelerated for 90 seconds t a speed of 0,2 /sec² beginning to the right Then he was rotated at a constant speed for 120 seconds, after which he was decelerated t a speed of 0,2 /sec² 120 seconds after stopping the same procedure was repeated, but this time in the opposite direction This procedure was conti ued with a simultaneous 0,2 /sec² increase in the speed of acceleration and deceleration for each new stage of acceleration and deceleration until continuous nystagmus was observed

The total amplitude during the acceleration of 1 /sec² up to the final speed of 60 /sec was also reckoned. Four otosclerotic patients whose threshold of angular acceleration was higher than 1 /sec² were excluded.

The postrotatory nystagmus was measured after an abrupt stop (0,5 sec) Before the stop the speed of rotation was maintained at 60 /sec. Calculations were made of the total amplitude and the maximum frequency for a period of ten seconds. If there was a

IV Material and methods

A. Material

The material of the study consists of 60 patients (31 females and 29 males) suffering from clinical otosclerosis. The patients were aged from 18 to 64 (the mean age being 4? years)

After the investigation they were all operated on at the Otolaryngological University Clinic in Turku in 1970—1971 The diagnosis of operation was otosclerosis in all sixty cases. Tissue samples were taken from ?0 patients for histopathological diagnosis. In eighteen cases the diagnosis was confirmed as otosclerosis in two cases the sample was too small to provide sufficient material for investigation. Cases with head trauma, any neurological disorders or any previous operations on the ear were totally excluded The distribution of the material according to age and sex is shown in table 1

The group of control subjects consists of nurses assistant nurses and other workers at the clinic, numbering ?0 in all The mean age of the control group was 40 individual ages varying between 27 and 50 Cases with anamnestic head trauma anamnestic vertigo or dizziness any neurological disorders or any anamnestic diseases of the ear were excluded. All control subjects had normal hearing The distribution of the control group according to age and sex is shown in table ..

Table 1 *D st b tio f the m terial ding t g nd*

Age years	Females N	%	Males No	%
10—20	1	3 2	1	3 5
21—30	3	9 7	6	20
31—40	9	29 0	11	37 9
41 50	9	29 0	4	13 8
51 -60	6	19 4	6	20 7
61—70	3	9 7	1	3 4
Total	31	100 0	29	100 0

Tabl *Distrib t f the t ol subje t ord g t ag d s*

Age years	Females N	%	Males No	%
20 30	3	18 7	–	
31 40	6	37 5		50 0
41 50		43 5	2	50 0
Total	16	100 0	4	100 0

B. Methods

1 Neuro-otological and audiological examination

The anamnesis was made as scrupulously as possible. Special attention was paid to any occurrence of otosclerosis in the patient's family to the duration of the symptoms, to any occurrence of vertigo or tinnitus and to the presence of paracusis. The patients were also submitted to neuro-otological investigation to exclude vertigo other than labyrinthine.

Air and bone conduction audiograms were measured by the usual descending ascending technique Speech thresholds and discrimination were determined for each patient as described by Palva (195?) Loudness recruitment was measured by Fowler method A Madsen OB-60 audiometer was used The audiometer was calibrated according to ISO Recommendation R 38?

? *Electronystagmographic investigation*

a Spontaneous and positional nystagmus

Any spontaneous r positional nystagmus was recorded in a dim room while the subject was lying with closed eyes

in a supine position
in both lateral positions and
with head hanging

The nystagmus findings were considered positive if the speed of the slow phase of the horizontal nystagmus exceeded 7°/sec.

The optokinetic nystagmus of the subjects was investigated at 30 and 60 /sec to the right and to the left alternately to exclude vertigo other than labyrinthine.

b Caloric tests

The caloric tests were performed according to Hallpike with the following exceptions The irrigation time was only 30 seconds. The induced nystagmus was recorded for 70 seconds while the subject kept his eyes closed Thus reaching the culmination phase was positively secured At the 70th second the subject was requested to open his eyes and to fix his gaze on a fixation light which was located approximately two metres directly in front of the subject. For each irrigation total amplitude and the angular velocity of the slow nystagmic phase during the culmination phase were calculated The result was considered canal paresis (unilateral hypoexcitability) when reactions before the fixation in one ear were 20 per cent weaker than those in the other ear Correspondingly the result was regarded as directional preponderance when the intensity of nystagmus with a tendency in one direction was 20 per cent greater than in the other All the subjects whose ocular fixation index (OFI) was higher than 50 per cent were excluded because in these subjects the origin of the nystagmus observed in ENG investigation might be other than labyrinthine (Demanez and Ledoux, 1970)

Silver silverchloride electrodes 7 mm in diameter were employed The two recording electrodes were located on the skin near the temporal canthi of the lids of the two eyes, the earthed electrode was placed on the skin of the forehead The electrodes were fixed with adhesive tape and electrode jelly was utilized to improve the contact DC differential amplifier direct ink writing (Elema mingograph) was employed Before and after every investigation the apparatus was calibrated by a ten degree movement of the eyes.

c. Rotatory tests

The rotatory tests were carried out by means of Polman's rotating chair (Polman Mod. 11 e 111) which enables linear adjustment of acceleration and deceleration speeds from 0,2 /sec² onwards The same type of electrode and the same pattern of fixating the electrodes were used as previously An A C. condenser coupled amplifier (Polman Mod MP 11) time constant 2 seconds, was utilized for the recording All recordings were performed in darkness. The subject's head was fixed tilted 30 degrees forward from the vertical

The linearity of acceleration and deceleration of the chair was controlled by the following method All the possible acceleration and deceleration speeds employed were investigated by accelerating and decelerating the chair for exactly 30, 60 and 90 seconds. After this the rotating time of the chair was measured as the mean time for 10 rotations The speed thus obtained was the same as the theoretical speed ± 5 per cent. Thus the linearity of acceleration and deceleration was confirmed.

The threshold of acceleration and deceleration was measured in the way described below The subject was accelerated for 90 seconds at a speed of 0,2 /sec² beginning to the right. Then he was rotated at a constant speed for 120 seconds, after which he was decelerated at a speed of 0,2 /sec² 120 seconds after stopping the same procedure was repeated, but this time in the opposite direction This procedure was continued with a simultaneous 0,2 /sec² increase in the speed of acceleration and deceleration for each new stage of acceleration and deceleration until continuous nystagmus was observed

The total amplitude during the acceleration of 1 /sec² up to the final speed of 60 /sec was also reckoned. Four otosclerotic patients whose threshold of angular acceleration was higher than 1 /sec² were excluded

The postrotatory nystagmus was measured after an abrupt stop (0,3 sec) Before the stop the speed of rotation was maintained at 60 /sec. Calculations were made of the total amplitude and the maximum frequency for a period of ten seconds If there was a

divergence of more than 20 per cent between nystagmus to the right and to the left the result was regarded as directional preponderance.

The statistical significances of all measurements mentioned above were counted by Student's t test and the contingency tables were tested using the Chi square test.

V Results

A. Anamnestic data

Anamnestic data on the patients are given in tables 3 and 4 Twenty-seven of the subjects examined (45 per cent) had close relatives (mother father brother or sister) with diagnosed otosclerosis. Thirty-nine patients (65 per cent) had suffered from hearing loss or tinnitus for at least five years before treatment Moreover 34 (57 per cent) cases complained anamnestically of brief periods of ertigo (not exceeding 30—60 seconds) during which they felt the horizon rocked and the world seemed to roll from side to side. According to many patients, these symptoms were associated with rapid move ments of the head, abrupt stops or with turns Many patients furthermore felt unsteadiness while walking in the dark or with their eyes closed Seventeen (28 per cent) patients complained of tinnitus and paracusis was anamnestically demonstrated in 50 per cent of the patients. The main reason for resorting to medical treatment was hearing loss in 53 cases (88 per cent) Tinnitus in one or both ears was given as the main reason by 7 pa tients (12 per cent) who also considered tinnitus more provoking than hearing loss

Table 3 *Anamnestic dat on patients suffering from otosclerosis*

	Otosclerosis in the family		Symptoms over five years		Anamnestic ertigo		Anamnestic tinnitus		Anamnestic paracusis	
	No	%	No	%	N	%	No	%	No	%
	27	45 0	39	65 0	34	56 7	17	28 3	30	50 0
—	33	55 0	21	35 0	26	43 3	43	71 7	30	50 0
Total	60	100 0	60	100 0	60	100 0	60	100 0	60	100 0

Table 4 *The subjects mean symptom befor treatment*

	No	%
Hearing loss	53	88 3
Tinnitus	7	11 7
Total	60	100 0

Table 5 *The average th shold of h aring in dB and standard deviations in the ont ol serie*

Hz	Right		Lef ear	
	mean	SD	mean	SD
125	5 5	4 4	9 5	7 4
250	6 0	3 9	8 5	6 4
500	5 0	4 6	10 0	7 3
1 000	2 5	5 8	8 0	5 9
2 000	2 0	6 3	6 5	8 8
4 000	9 0	6 3	12 0	9 8
6 000	1 0	4.5	7 5	11 5
8 000	4 0	6.7	7 0	10 5

B. Hearing results

a. Control series

The hearing results for the control subjects are shown in table 5 and figure 1 The aver age hearing results are given in dB and are to be considered normal in relation to the age of the subject in question The discrimination ability of all the control subjects was established as 100 per cent.

b. Clinical otosclerosis

The results are presented in tables 6 and 7 and in figures 2 and 3. The mean hearing loss (air conduction and bone conduction) in the right and in the left ear at arious frequencies and the corresponding values of

divergence of more than 20 per cent between nystagmus to the right and to the left the result was regarded as directional preponderance.

The statistical significances of all measurements mentioned above were counted by Student's t test and the contingency tables were tested using the Chi square test.

V Results

A. Anamnestic data

Anamnestic data on the patients are given in tables 3 and 4 Twenty-seven of the subjects examined (45 per cent) had close relatives (mother father brother or sister) with diagnosed otosclerosis. Thirty-nine patients (65 per cent) had suffered from hearing loss or tinnitus for at least five years before treatment Moreover 34 (57 per cent) cases complained anamnestically of brief periods of vertigo (not exceeding 30—60 seconds) during which they felt the horizon rocked and the world seemed to roll from side to side. According to many patients, these symptoms were associated with rapid movement of the head, abrupt stops or with turns. Many patients furthermore felt unsteadiness while walking in the dark or with their eyes closed Seventeen (28 per cent) patients complained of tinnitus and paracusis was anamnestically demonstrated in 50 per cent of the patients. The main reason for resorting to medical treatment was hearing loss in 53 cases (88 per cent) Tinnitus in one or both ears was given as the main reason by 7 patients (12 per cent) who also considered tinnitus more provoking than hearing loss

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	No	%	No	%	No	%	No	%	No	%
+	27	45 0	39	65 0	34	56 7	17	28 3	30	50 0
−	33	55 0	21	35 0	26	43 3	43	71 7	30	50 0
Total	60	100 0	60	100 0	60	100 0	60	100 0	60	100 0

Table 4 *The subjects main symptom before treatment*

	No	%
Hearing loss	53	88 3
Tinnitus	7	11 7
Total	60	100 0

Table 5 *The average thresholds of hearing in dB and standard deviations in the control series*

Hz	Right	a.c	Left ear	c.
	mean	SD	mean	SD
125	5 5	4 4	9 5	7 4
250	6 0	3 9	8 5	6 4
500	5 0	4 6	10 0	7 3
1 000	2 5	5 8	8 0	5 9
2 000	2 0	6 3	6 5	8 8
4 000	9 0	6 3	12 0	9 8
6 000	1 0	4 5	7 5	11 5
8 000	4 0	6 7	7 0	10 5

B. Hearing results

a. Control series

The hearing result for the control subjects are shown in table 5 and figure 1 The average hearing results are given in dB and are to be considered normal in relation to the age of the subject in question. The discrimination ability of all the control subjects was established as 100 per cent.

b Clinical otosclerosis

The results are presented in tables 6 and 7 and in figures 2 and 3. The mean hearing loss (air conduction and bone conduction) in the right and in the left ear at various frequencies and the corresponding values of

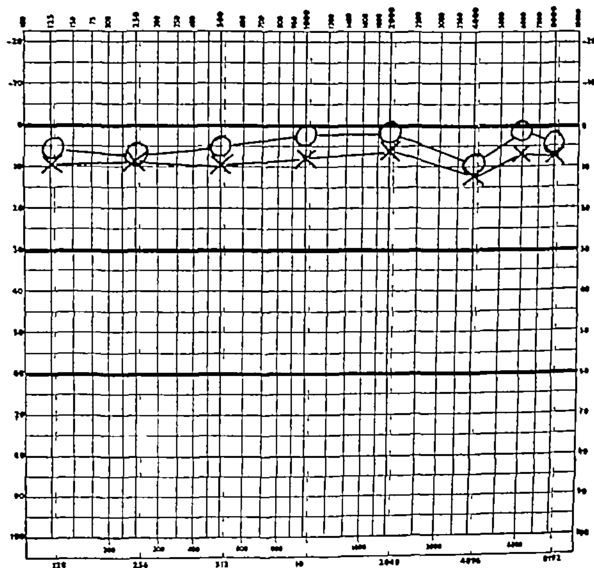


Fig. 1

The mean audiogram in control series
O = right ear air conduction
X = left ear air conduction

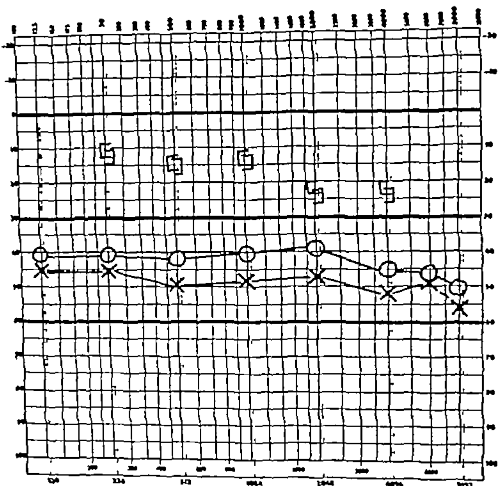
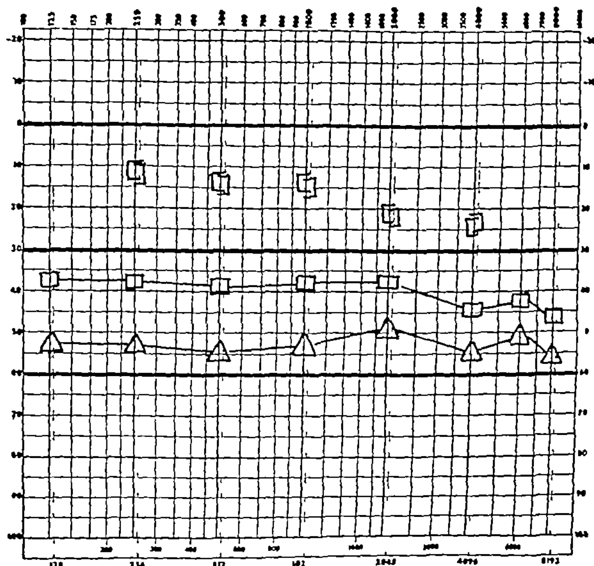


Fig 2

The mean audiogram of right and left ear in patients suffering from otosclerosis
O = right ear air conduction
X = left ear air conduction
[= right ear bone conduction
] = left ear bone conduction



F g 3

The mean audiogram of the better ea and the worse ear in patients suffering from otosclerosis
□ = better ear ai cond ction
Δ = worse ea ai conduction
[= better ear bone conduction
] = w rse ear bon conduction

standard deviation, maximum and minimum hearing loss are given in table 6. Figure 2 presents the hearing results as an audiogram Table 7 shows the mean hearing loss (air conduction and bone conduction) and the other values mentioned above in the better ear and in the worse ear (the ear which is t be operated on) The corresponding audiogram is shown in figure 3

The hearing loss (air conduction) in the ear to be operated on was 48—56 dB on an average and that in the better ear approximately 37—47 dB The bone conduction hearing alues were correspondingly 10—25 dB in the worse ear and 10—20 dB in the better The average air bone gap was approximately 35 dB in the worse ear and about 20 dB in the better ear

Table 6 A erage hearing result of right and left ear in patient suffering from otos lerosis (the alues given are mean standard deviation max im m hearing loss, mi imum hearing loss)

Hz		Righ ear		Lef ear	
			b		b
125	MEAN	41 8		45 2	
	SD	19 2		15 2	
	MAX	75 0		75 0	
	MIN	5 0		5 0	
250	MEAN	41 5	11 8	45 7	13 2
	SD	20 3	6 2	15 1	6 6
	MAX	80 0	30 0	75 0	30 0
	MIN	5 0	5 0	5 0	5 0
500	MEAN	42 7	14 3	49 1	15 5
	SD	21 4	7 4	15 4	7 9
	MAX	90 0	30 0	90 0	35 0
	MIN	5 0	5 0	5 0	5 0
1000	MEAN	40 8	13 1	47 0	14 9
	SD	20 8	8 0	15 7	8 3
	MAX	90 0	40 0	80 0	35 0
	MIN	5 0	5 0	5 0	5 0
2000	MEAN	38 6	22 0	44 2	25 9
	SD	20 2	13 7	19 0	13 9
	MAX	90 0	60 0	90 0	60 0
	MIN	5 0	5 0	5 0	5 0
4000	MEAN	45 1	22 0	52 8	24 1
	SD	22 1	13 3	20 2	13.1
	MAX	90 0	50 0	90 0	50 0
	MIN	5 0	5 0	5 0	5 0
6000	MEAN	42 5		47 7	
	SD	23 1		24 2	
	MAX	90 0		90 0	
	MIN	5 0		5 0	
8000	MEAN	46 3		5. 4	
	SD	25 1		25 6	
	MAX	90 0		90 0	
	MIN	5 0		5 0	

The better ear was considered to be clinically healthy in seventeen patient because the air and bone conduction values were better than 10 dB at each frequency studied.

Speech reception thresholds correlated with the pure tone air conduction values, and speech perception exceeded 90 % in all cases. Recruitment as measured according to Fowler was verified in 7 patients (15 per

Table 7 A erage hearing result of the better ear and the worse ear patient suffering from ot sclerosis (the alues given are mean standard deviation maximum hearing loss minimum h aring loss)

Hz		Better ear		Worse ear	
			b		b
125	MEAN	37 7		53 6	
	SD	21.2		11.5	
	MAX	75 0		75 0	
	MIN	5 0		30 0	
250	MEAN	37 4	11.3	53 0	11 8
	SD	23 2	5 4	14 9	5 9
	MAX	80 0	25 0	80 0	25 0
	MIN	5 0	5 0	.5 0	5 0
500	MEAN	38 4	13 2	54 6	14 0
	SD	25 6	7 7	17.9	8 0
	MAX	90 0	30 0	90 0	30 0
	MIN	5 0	5 0	10 0	5 0
1000	MEAN	37.5	13 5	53 2	14 8
	SD	23 6	9 5	17 0	9 8
	MAX	90 0	40 0	90 0	40 0
	MIN	5 0	5 0	10 0	5 0
2000	MEAN	37 0	21 0	48 2	23.2
	SD	23 7	14 7	18 2	12 9
	MAX	90 0	55 0	90 0	55 0
	MIN	5 0	5 0	15 0	5 0
4000	MEAN	44 9	24 0	54 8	23 8
	SD	21 8	14 8	21 1	13 2
	MAX	90 0	50 0	90 0	50 0
	MIN	5 0	5 0	10 0	5 0
6000	MEAN	43 5		52 2	
	SD	24 4		22 5	
	MAX	90 0		90 0	
	MIN	5 0		25 0	
8000	MEAN	46 8		55 8	
	SD	25 2		21.9	
	MAX	90 0		90 0	
	MIN	5 0		15 0	

Table 8 *Recruitment as measured according to Fowler in patients suffering f om otosclerosis.*

	N	%
Recruitment	7	14 6
N recruitment	41	85 4
Total	48	100 0

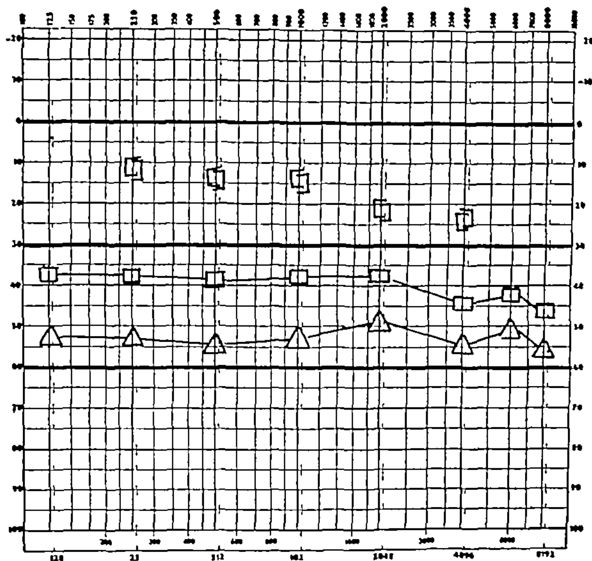


Fig. 3

The mean audiogram of the better ear and the worse ear in patients suffering from otosclerosis.
□ = better ear air conduction
△ = worse ear air conduction
[= better ear bone conduction
] = worse ear bone conduction

standard deviation, maximum and minimum hearing loss are given in table 6. Figure 2 presents the hearing results as an audiogram. Table 7 shows the mean hearing loss (air conduction and bone conduction) and the other alues mentioned abov in the better ear and in the worse ear (the ear which is to be operated o) The corresponding audiogram is shown in figure 3.

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Table 6 *Average hearing esults of right and left ear in patients suffering from otosclerosis (the alues given are mean, standard deviation max im m hearing loss minim m hearing loss)*

Hz		Right ear		Left ear	
			b c	a	b
125	MEAN	41 8		45 2	
	SD	19 2		15 2	
	MAX	75 0		75 0	
	MIN	5 0		5 0	
250	MEAN	41 5	11 8	45 7	13 2
	SD	20 3	6 2	15 1	6 6
	MAX	80 0	30 0	75 0	30 0
	MIN	5 0	5 0	5 0	5 0
500	MEAN	42 7	14 3	49 1	15 5
	SD	21 4	7 4	15 4	7.9
	MAX	90 0	30 0	90 0	35 0
	MIN	5 0	5 0	5 0	5 0
1000	MEAN	40 8	13 1	47 0	14 9
	SD	20 8	8 0	15 7	8 3
	MAX	90 0	40 0	80 0	35 0
	MIN	5 0	5 0	5 0	5 0
2000	MEAN	38 6	22 0	44 2	23 9
	SD	20 2	13 7	19 0	13 9
	MAX	90 0	60 0	90 0	60 0
	MIN	5 0	5 0	5 0	5 0
4000	MEAN	45 1	22 0	52 8	24 1
	SD	22 1	13 3	20 2	13 1
	MAX	90 0	50 0	90 0	50 0
	MIN	5 0	5 0	5 0	5 0
6000	MEAN	42 5		47 7	
	SD	23 1		24 2	
	MAX	90 0		90 0	
	MIN	5 0		5 0	
8000	MEAN	46 3		52 4	
	SD	25 1		25 6	
	MAX	90 0		90 0	
	MIN	5 0		5 0	

The better ear was considered to be clinically healthy in seventeen patients because the air and bone conduction values were better than 10 dB at each frequency studied.

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Table 7 *A er g hear g ult of the better er and the worse er patient suffering from otosclerosis (the value given ar mean standard deviation maxim m hearing loss minim m hearing loss)*

		Better ear		Worse ear	
Hz		a	b	c	b c
125	MEAN	37 7		53 6	
	SD	21.2		11.5	
	MAX	75 0		75 0	
	MIN	5 0		30 0	
250	MEAN	37 4	11 3	53 0	11 8
	SD	23 2	5 4	14 9	5 9
	MAX	80 0	25 0	80 0	25 0
	MIN	5 0	5 0	25 0	5 0
500	MEAN	38 4	13 2	51 6	14 0
	SD	25 6	7 7	17.9	8 0
	MAX	00 0	30 0	90 0	30 0
	MIN	5 0	5 0	10 0	5 0
1000	MEAN	3 5	13 5	53 2	14 8
	SD	25 6	9 5	17 0	9 8
	MAX	90 0	40 0	90 0	40 0
	MIN	5 0	5 0	10 0	5 0
2000	MEAN	37 0	21 0	48 2	23.2
	SD	23 7	14 7	18 2	12 9
	MAX	90 0	55 0	90 0	55 0
	MIN	5 0	5 0	15 0	5 0
4000	MEAN	44 9	24 0	54 8	23 8
	SD	21 8	14 8	21 1	13 2
	MAX	90 0	50 0	90 0	50 0
	MIN	5 0	5 0	10 0	5 0
6000	MEAN	43 5		52 2	
	SD	24 4		22 5	
	MAX	90 0		90 0	
	MIN	5 0		25 0	
8000	MEAN	46 8		55 8	
	SD	26 2		21 9	
	MAX	90 0		90 0	
	MIN	5 0		15 0	

Table 8 *Recruitment as measured according to Fowler in patients suffering f om otosclerosis*

	No	%
Recruitment	7	14 6
N recruitment	41	85 4
Total	48	100 0

Table 9 *D ecti nal preponderance and hypoexci bility (anal paresis) in the c nt ol seri s measur d from maxim m eye speed s mm d mplitud s d f om the two joi tly*

	Maximum amplitude		Summed amplitude		The two jointly	
	No.	%	No.	%	No.	%
Directional preponderance	2	10	1	5	1	5
Hypoexcitability (canal paresis)	0	0	1	5	0	0
Normal caloric response	18	90	18	90	19	95
Total	20	100	20	100	20	100

cent from total 48) Forty-eight patients of sixty were studied by this method Table 8

C. Electronystagmographic findings

a. Control series

1—4 Positional nystagmus caloric tests rotatory tests and postrotatory nystagmus

Examinations with Frenzel s glasses or electronystagmography did not reveal any perceptible nystagmus.

In caloric tests two subjects showed directional preponderance as measured from maximum eye speed. One of them showed directional preponderance even as measured from total amplitude.

Reduced caloric excitability was demonstrated in one subject as measured from *total amplitude Yet no divergence was* perceived in caloric excitability between the two ears when the maximum eye speed was being measured The results are given in table 9

The threshold of angular acceleration and deceleration in the control series are shown in table 10 which likewise presents the standard deviation and the highest and lowest thresholds of acceleration and deceleration observed in this group When stopping abruptly from the speed of 60 /sec. the following mean summed amplitudes of the slow phase of the first postrotatory nystagmus in control series were manifested 119 right nystagmus beating and 117 left beating The maximum frequency for a period of ten seconds was correspondigly 18,2 nystagmus beatings to the right and 19,2 to the left

Table 10 *The th esholds of angular celeration and d celeratio d ri g rot tory tests (exp essed i degrees/s c²) Me standard dev ation m x mum and m n m m val es*

	Acceleration to the right	Deceleration to the right	Acceleration t the left	Deceleration t the left
MEAN	0 37	0 33	0.3	0 37
SD	0 13	0 07	0 10	0 1
MAX	0.60	0.50	0 40	0 60
MIN	0 20	0.30	0 20	0 30

Table 11 *Appear nce f nyst gm observed with Fr zel's glass s Cases with cli cal tosclerosi*

	N	%
Nystagmus observed	5	8 3
N nystagmus observed	55	91 7
Total	60	100 0

Tabl 12 *App aran f nyst gm b erv d by el ctro yst gm gr phy*

	N	%
Nyst gmu observed	20	33 3
N stagmu observed	40	66 7
T tal	60	100 0

Table 13 *Types of yst gm f d by le t o y t gm gr phy*

Type of nystagmus	N	%
D rection-changi g (Nylén type I)	5	5
Direction-det rmined (Nylén type II)	14	70
Irregular d rection-changing (Nylén type III)	1	5
Total	20	100 0

Table 14 *Directional preponderance and hypoexcitability in the caloric test in patients suffering from otosclerosis as measured from maximum eye speed summed amplitude and the two jointly*

	Maximum eye speed No	%	Summed amplitude No.	%	The two jointly No.	%
Directional preponderance	29	48 3	32	53 3	22	36 7
Hypoexcitability (canal paresis)	34	56 7	33	55	25	41 7

b Clinical otosclerosis

1 Positional nystagmus

Positional nystagmus was observed with Frenzels glasses in five patients suffering from otosclerosis (8,3 per cent) The results are given in table 11 By electronystagmography the nystagmus was recorded in 20 patients (33,3 per cent) Five of these (25 per cent) revealed direction-changing (Nylen type I) fourteen (70 per cent) showed direction-determined (Nylen s type II) and one patient (5 per cent) showed irregular direction-changing (Nylen type III) nystagmus (Aschan et al 1956) These results are shown in tables 12 and 13

2 Caloric tests

I the caloric tests directional preponderance was observed in 29 patients (48,3 per cent) as measured from maximum eye speed and in 32 patients (53,3 per cent) as measured from total amplitude Directional preponderance occurred in 22 patients (36.7 per cent) when measured from maximum eye speed and total amplitude jointly I ten of these it was on the side of the better ear and in twelve cases on the side of the worse ear

Thirty four patients (56,7 per cent) revealed unilateral hypoexcitability in caloric tests as measured from maximum eye speed and 33 patients (55 per cent) as measured from total amplitude Unilateral hypoexcitability in the caloric tests was manifested in 25 patients (41 7 per cent) when measured from maximum eye speed and total amplitude jointly I twelve of these it was in the ear with better hearing and in thirteen cases in the poorer ear The results are shown in table 14

Directional preponderance was consequently observed significantly more frequently in patients suffering from otosclerous than in control subjects ($p < 0{,}01$ when measured from maximum eye speed and $p < 0{,}001$ when measured from total amplitude) Caloric hypoexcitability was even found in otosclerotic patients to a significantly greater degree than in healthy subjects ($p < 0{,}001$ when measured from total amplitude)

3 Rotatory tests

The thresholds of angular acceleration and deceleration for patients suffering from otosclerosis are presented in table 15. To facilitate reading table 16 gives a combination of the two preceding tables presenting the mean thresholds in the two groups parallelly Table 16 also includes the standard deviation, the t-test values and any significance (p) I the control series, the threshold of acceleration to the right was 0,37 °/sec² and to the left 0,32 °/sec² The thresholds of deceleration correspondingly showed the following values 0,33°/sec² to the right and 0,37 °/sec² to the left These differences are not statistically significant

Table 15 *Patients suffering from otosclerosis The thresholds of angular acceleration and deceleration during rotatory test (expressed in deg/sec²) SD standard deviation maximum and minimum values*

	Acceleration to the right	Deceleration to the right	Acceleration to the left	Deceleration to the left
MEAN	0 49	0 58	0 60	0 50
SD	0 33	0 33	0 28	0 28
MAX	2 00	2 00	1.50	2 00
MIN	0 20	0 20	0 20	0 30

Table 16 *Comparison between the thresholds of angular acceleration and deceleration in the control subjects and in otosclerotic patients The mean thresholds expressed in degrees/sec²*

		MEAN	SD	T	P
The threshold of angular acceleration to the right	Control series	0.37	0 13	2.276	0 05
	Otoscl. patients	0 49	0.33		
The threshold of angular deceleration to the right	Control series	0 33	0 07	5 490	0 001
	Otoscl. patients	0 58	0.33		
The threshold of angular acceleration to the left	Control series	0.32	0 10	6 532	0 001
	Otoscl. patients	0 60	0 28		
The threshold of angular deceleration to the left	Control series	0.37	0 12	2.799	0 01
	Otoscl. patients	0 50	0 28		

The corresponding values of thresholds for patients suffering from otosclerosis were 0 49 /sec² to the right and 0 60 /sec² to the left during the acceleration phase. The thresholds of deceleration showed the following values 0,58 /sec² to the right and 0 50 /sec² to the left The differences are not statistically significant, either However the threshold of angular acceleration and deceleration in the control group is significantly lower than the values established in the patients suffering from otosclerosis (table 16) The threshold of angular acceleration to the right was as low as 0 37 /sec² in the control series while the prevailing value for the patients was as high as 0 49°/sec² ($p < 0\ 05$) Correspondingly the thresholds of acceleration to the left gave the values 0,32 /sec² and 0 60 /sec² ($p < 0\ 001$) The thresholds of deceleration to the right were parallelly 0 33 /sec² and 0,58 /sec² ($p < 0\ 001$) while the values of the thresholds when decelerating to the left were 0 37 /sec² and 0,50 /sec² ($p < 0\ 01$)

Table 17 shows the thresholds of angular acceleration and deceleration in the affected and in the clinically healthy ear in the seventeen patients with clinical otosclerosis in one ear only The thresholds of acceleration in the affected ear was 0 68 /sec² and in the healthy ear 0 54 /sec² The corresponding values for the deceleration thresholds were 0,56 /sec² and 0 67 /sec² These differences are however not statistically significant The thresholds in these patients are significantly higher than the corresponding values established in the control group though, ($p < 0\ 01$) The joint mean threshold of acceleration in the control series (calculated from the right and the left side jointly) was 0 35 /sec² the joint mean threshold of deceleration showing precisely the same value (0,35 /sec²)

Table 18 presents a comparison between the values.

Table 19 shows the mean thresholds of angular acceleration and deceleration to the side of the more affected ear (0,56 /sec² and 0,53 /sec²) and to the side of the better ear (0,53 /sec² and 0,54 /sec²) in patients suffering from otosclerosis. There are no statistically significant differences between the two sides. The differences between the joint mean thresholds of the control subjects (0,35 /sec²) and patients suffering from otosclerosis are, however highly significant ($p < 0\ 001$) The comparison is presented in table 20

Table 17 *The m[illegible] th[illegible]shold of angul[illegible] [illegible]eration [illegible] d[illegible] d[illegible]el[illegible]ation (st[illegible]dard d[illegible] [illegible] m[illegible]xim[illegible]m [illegible]d minimum value) [illegible] the [illegible] of the aff[illegible]ted and the healthy ea[illegible] [illegible] the 17 patients [illegible] had cli[illegible]al oto[illegible]ler[illegible]s[illegible] in [illegible] (Th[illegible] m[illegible] [illegible] exp[illegible]ssed in d[illegible]gr[illegible]/[illegible])*

	Acceleration to the side of the affected ear	Deceleration to the side of the affected ear	Acceleration to the side of the healthy ear	Deceleration to the side of the healthy ear
MEAN	0 68	0 56	0 54	0 67
SD	0 35	0 25	0 26	0 17
MAX	1 50	1 00	1 00	2 00
MIN	0 20	0 30	0 20	0 30

Table 18 *Comparison betw en the mean threshold of angular acceleration and deceleration t the side of the affected ear and t the sd of the healthy ar in patients suffer g from otosclerosis on ear ul) (17 cases) and the mea threshold prevailing in th control subject (Mean threshold pressed in d grees/sec²)*

		MEAN	SD	T	P
The threshold of angular acceleration to the side of the affected ear	otoscl patients	0 68	0 35	3.73	0 01
The mean threshold of angular acceleration to the right and the left	control subjects	0 35	0 12		
The threshold of angular deceleration to the side of the affected ear	otoscl patients	0 56	0 25	3.30	0 01
The mean threshold of angular deceleration to the right and the lef	control subjects	0 35	0 10		
The threshold of angular acceleration to the side of the healthy ear	otoscl patients	0 54	0 26	2 89	0 01
The mean threshold of angular acceleration to the right and the lef	control subjects	0 35	0.12		
The threshold of angular deceleration to the side of the healthy ear	otoscl patients	0 67	0.47	2 83	0 01
The mean threshold of angular deceleration to the right and the lef	control subjects	0.35	0 12		

Table 19 *The mean thresholds standard deviations nd maximum and minim m values of angular ac eleration and d celeration to the side f the more affec d ar and to the side of the better ar in patient suffering from otosclerosis (60 ases) (esults expressed in d grees/sec²)*

	Acceleration to the side of the more affected ear	Deceleration to the side of the more affected ear	Acceleration to the side of better ear	Deceleration to the side of better ear
MEAN	0 56	0 53	0 53	0 54
SD	0 31	0 30	0 31	0 32
MAX	1 50	2 00	2 00	2 00
MIN	0 20	0 30	0 20	0 20

When the acceleration of one degree/sec² from zero to the speed of 60 /sec to the right and to the left was employed — the speed is approximately 0,5 /sec² higher tha the mean threshold of acceleration, — there were no statistically significant differences between the total amplitudes of the slow phase of nystagmus in the control subjects and in patients suffering from otosclerous. The results are presented in table 21 The mean total amplitude during acceleration to the right was 108 In the control subjects while the corresponding value in patients suf fering from otosclerosis was shown to be 101 Correspondingly the alues when ac

Table 16. *Comparison between the thresholds of angular acceleration and deceleration in the control subjects and in otosclerotic patients. The mean thresholds expressed in degrees/sec²*

		MEAN	SD	T	P
The threshold of angular acceleration to the right	Control series	0.37	0.13	2.226	0.05
	Otoscl. patients	0.49	0.33		
The threshold of angular deceleration to the right	Control series	0.33	0.07	5.490	0.001
	Otoscl. patients	0.58	0.33		
The threshold of angular acceleration to the left	Control series	0.32	0.10	6.53	0.001
	Otoscl. patients	0.60	0.28		
The threshold of angular deceleration to the left	Control series	0.37	0.1[illegible]	2.799	0.01
	Otoscl. patients	0.50	0.[illegible]8		

The corresponding values of thresholds for patients suffering from otosclerosis were 0.49 °/sec² to the right and 0.60 °/sec² to the left during the acceleration phase. The thresholds of deceleration showed the following values: 0,58 °/sec² to the right and 0,50 °/sec² to the left. The differences are not statistically significant either. However the threshold of angular acceleration and deceleration in the control group is significantly lower than the values established in the patients suffering from otosclerosis (table 16). The threshold of angular acceleration to the right was as low as 0,37 °/sec² in the control series while the prevailing value for the patients was as high as 0.49 °/sec² ($p < 0,05$). Correspondingly the thresholds of acceleration to the left gave the values 0.32 °/sec² and 0.60 °/sec² ($p < 0.001$). The thresholds of deceleration to the right were parallelly 0,33 °/sec² and 0.58 °/sec² ($p < 0.001$) while the values of the thresholds when decelerating to the left were 0.37 °/sec² and 0.50 °/sec² ($p < 0.01$).

Table 17 shows the thresholds of angular acceleration and deceleration in the affected and in the clinically healthy ear in the seventeen patients with clinical otosclerosis in one ear only. The thresholds of acceleration in the affected ear was 0.68 °/sec² and in the healthy ear 0.54 °/sec². The corresponding values for the deceleration thresholds were 0.56 °/sec² and 0.67 °/sec². These differences are however not statistically significant. The thresholds in these patients are significantly higher than the corresponding values established in the control group though, ($p < 0.01$). The joint mean threshold of acceleration in the control series (calculated from the right and the left side jointly) was 0,35 °/sec², the joint mean threshold of deceleration showing precisely the same value (0.35 °/sec²).

Table 18 *presents a comparison between* the values.

Table 19 shows the mean thresholds of angular acceleration and deceleration to the side of the more affected ear (0,56 °/sec² and 0,53 °/sec²) and to the side of the better ear (0.53 °/sec² and 0,54 °/sec²) in patients suffering from otosclerosis. There are no statistically significant differences between the two sides. The differences between the joint mean thresholds of the control subjects (0,35 °/sec²) and patients suffering from otosclerosis are, however, highly significant ($p < 0.001$). The comparison is presented in table 20.

Table 17. *The mean thresholds of angular acceleration and deceleration (standard deviation and maximum and minimum values) to the side of the affected and the healthy ear of the 17 patients who had clinical otosclerosis in one ear only. (The mean values expressed in degrees/sec²)*

	Acceleration to the side of the affected ear	Deceleration to the side of the affected	Acceleration to the side of the healthy ear	Deceleration to the side of the healthy ear
MEAN	0.68	0.56	0.54	0.6[illegible]
SD	0.33	0.[illegible]5	0.36	0.[illegible]
MAX	1.50	1.00	1.00	[illegible].00
MIN	0.20	0.30	0.20	0.30

Table 18 *Comparison between the mean threshold of angular acceleration and deceleration to the side of the affected ear and to the side of the healthy ear in patients suffering from otosclerosis in one ear only (17 cases) and the mean threshold prevailing in the control subjects (Mean threshold expressed in degrees/sec²)*

		MEAN	SD	T	P
The threshold of angular acceleration to the side of the affected ear	otoscl patients	0 68	0 35	3.75	0 01
The mean threshold of angular acceleration to the right and the left	control subjects	0 35	0.12		
The threshold of angular deceleration to the side of the affected ear	otoscl patients	0 56	0 25	3 30	0 01
The mean threshold of angular deceleration to the right and the lef	control subjects	0 35	0 10		
The threshold of angular acceleration to the side of the healthy ear	otoscl patients	0 54	0 26	2 89	0 01
The mean threshold of angular acceleration to the right and the lef	control subjects	0 35	0.12		
The threshold of angular deceleration to the side of the healthy ear	otoscl patients	0 67	0 47	2 85	0 01
The mean threshold of angular deceleration to the right and the left	control subjects	0 35	0 12		

Table 19 *The mean thresholds standard deviation and maximum and minimum values of angular acceleration and deceleration to the side of the more affected ear and to the side of the better ear in patients suffering from otosclerosis (60 cases) (Results expressed in degrees/sec²)*

	Acceleration to the side of the more affected ear	Deceleration to the side of the more affected ear	Acceleration to the side of better ear	Deceleration to the side of better ear
MEAN	0 56	0 53	0 53	0 54
SD	0 31	0 30	0 31	0 32
MAX	1 50	2 00	2 00	2 00
MIN	0 20	0 30	0 20	0 20

When the acceleration of one degree/sec² from zero to the speed of 60 /sec to the right and to the left was employed — the speed is approximately 0,5 /sec² higher than the mean threshold of acceleration, — there were no statistically significant differences between the total amplitudes of the slow phase of nystagmus in the control subjects and in patients suffering from otosclerosis. The results are presented in table 21 The mean total amplitude during acceleration to the right was 108 in the control subjects while the corresponding value in patients suffering from otosclerosis was shown to be 101 Correspondingly the values when ac

Table 16 *Comparison between the thresholds of angular acceleration and deceleration in the control subjects and in otosclerotic patients. The mean thresholds expressed in degrees/sec²*

		MEAN	SD	T	P
The threshold of angular acceleration to the right	Control series	0.37	0.13	2.276	0.05
	Otoscl. patients	0.49	0.33		
The threshold of angular deceleration to the right	Control series	0.33	0.07	3.490	0.001
	Otoscl. patients	0.58	0.33		
The threshold of angular acceleration to the left	Control series	0.32	0.10	6.53	0.001
	Otoscl. patients	0.60	0.28		
The threshold of angular deceleration to the left	Control series	0.37	0.12	2.799	0.01
	Otoscl. patients	0.50	0.28		

The corresponding values of thresholds for patients suffering from otosclerosis were *0.49 /sec² to the right and 0.60 /sec² to the left* during the acceleration phase. The thresholds of deceleration showed the following values 0,58 /sec² to the right and 0,50 /sec² to the left. The differences are not statistically significant either. However the threshold of angular acceleration and deceleration in the control group is significantly lower than the values established in the patients suffering from otosclerosis (table 16). The threshold of angular acceleration to the right was as low as 0,37 /sec² in the control series while the prevailing value for the patients was as high as 0.49°/sec² ($p < 0.05$). Correspondingly the thresholds of acceleration to the left gave the values *0,32 /sec² and 0.60 /sec² ($p < 0.001$)*. The thresholds of deceleration to the right were parallelly 0.33 /sec² and 0,58 /sec² ($p < 0.001$) while the values of the thresholds when decelerating to the left were 0.37 /sec² and 0,50 /sec² ($p < 0.01$).

Table 17 shows the thresholds of angular acceleration and deceleration in the affected and in the clinically healthy ear in the seventeen patients with clinical otosclerosis in one ear only. The thresholds of acceleration in the affected ear was 0.68 /sec² and in the healthy ear 0.54 /sec². The corresponding values for the deceleration thresholds were 0.56 /sec² and 0.67 /sec². These differences are, however, not statistically significant. The thresholds in these patients are significantly higher than the corresponding values established in the control group though ($p < 0.01$). The joint mean threshold of acceleration in the control series (calculated from the right and the left side jointly) was 0,35 /sec² the joint mean threshold of deceleration showing precisely the same value (0,35 /sec²).

Table 18 presents a comparison between the values.

Table 19 shows the mean thresholds of angular acceleration and deceleration to the side of the more affected ear (0,56 /sec² and 0,53 /sec²) and to the side of the better ear (0,53 /sec² and 0.54 /sec²) in patients suffering from otosclerosis. There are no statistically significant differences between the two sides. The differences between the joint mean thresholds of the control subjects (0.35 /sec²) and patients suffering from *otosclerosis are, however highly significant* ($p < 0.001$). The comparison is presented in table 20.

Table 17 *The mean thresholds of angular acceleration and deceleration (standard deviation and maximum and minimum values) to the side of the affected and the healthy ear of the 17 patients who had clinical otosclerosis on one side. (The mean values expressed in degrees/sec²)*

	Acceleration to the side of the affected ear	Deceleration to the side of the affected ear	Acceleration to the side of the healthy ear	Deceleration to the side of the healthy
MEAN	0.68	0.56	0.54	0.67
SD	0.33	0 5	0.26	0.17
MAX	1.50	1.00	1.00	00
MIN	0.20	0.30	0.20	0.30

phase of nystagmus when accelerating at a rate of one degree/sec^2 from zero to 60 /sec to the side of the more affected ear were 95 and to the side of the better ear 96 In patients suffering from otosclerosis. In the control subjects the mean summed amplitude to the right was 108 which is precisely the same value as that obtained from the left side The difference is not statistically signi ficant The results are presented in table 23.

Table 23 *The mean summed amplit des of the slow phase of nyst gmus by using rat of degree/se f angular acceleration f om zero t 60°/sec t the sid of the more aff cted ear and to the side of the bett er in patients suffering from otosclerosis (total 56 patients) and t the right and the left in the ontrol subjects (total 40 accelerations) Mean alues pressed in degrees*

Otoscler patients		Otoscler patients	Control subjects
Acceleration to the side of the more affected ear		Acceleration to the side of the better ear	Mean accel- eration the right and the left
MEAN	95	96	108
SD	66	63	41
MAX	320	345	200
MIN	20	36	45

4 *P st otatory ystagmus*

When stopping abruptly from the speed of 60°/sec. the following mean summed ampli tudes of the slow phase of the first post rotatory nystagmus in control series were manifested 119 right nystagmus beating and 117 left beating The corresponding mean alues for patients suffering from oto- sclerosis were 120 and 118 (table 24) The maximum frequency for period of ten seconds was correspondingly in control series 18, nystagmus beatings to the right and 19,2 to the left otosclerotic patient showed the alues of 18,3 ny tagmu beatings to the right and 18,6° beatings to the left Thu there were no satistically significant d fferen ces between the two ides or between the control series and the grou of otosclerotic patie ts

In patients suffering from unilateral oto- sclerosis (17 cases) the summed amj litude of the slow phase of the first postrotatory nystagmus after an abrupt stop from the speed of 60 /sec was 116° to the side of the affected ear and 1 1 to the side of the healthy ear

Correspondingly the mean summed ampli- tudes of the slow phase of the first post rotatory nystagmus were 108 to the side of the more affected ear and 116 to the side of the better ear in the whole group of pa tients suffering from otosclerosis (60 cases) The postrotatory nystagmus to the side of the more affected ear in both groups was weaker than that to the side of the better ear but no pronounced statistical singificance could be established

D Comparison between audiological and electronystagmographical findings

The hearing of both ears at all frequencies studied wa found to be worse in the patients who showed spontaneous or positional nystagmus in the electronystagmographic in- vestigation (20 p tient) than in those cases who showed no nystagmus ir the above in vestigation (40 patient) In the higher fre quency range the difference between the groups with nystagmus and with no nystag mus greater though statistically significant differences were not demonstrated except n the left ear t 4 000 Hz in bone con duction (p <0,05) and at 4 000 H and

Table 24 *The mean summed amplitudes of the slow phase f the first postrotatory nyst gmus t the right and the left after an abrupt stop from the peed of 60°/sec. Comparison between control series and patient suffering from otosclerosis Mean alue pressed in degrees*

		MEAN	SD	T	P
The first postrotatory nystagmus to the right	Control subjects	119	60		
	Otoscl patients	120	90	0 064	—
The first postrotatory nystagmus to the lef	Control subjects	117	60		
	Otoscl. patients	118	96	0 036	—

Table 20 *Comparison between the mean thresholds of angular accele a ion and d celeration to the side of the more ffected ear and to the side of the better ear in p tients suff ring f om otosclerosis and the mean threshold of angular acceler tion and deceleration to the right and the left in co trol subjects (expressed in degrees/sec²)*

		MEAN	SD	T	P
The threshold of angular acceleration to the side of the more affected ear	otoscl. patients	0.56	0 31	4 71	0 001
The threshold of angular acceleration mean to the right and the left	control subjects	0.35	0 1?		
The threshold of angula deceleration to the side of the more affected ear	otoscl patients	0.53	0.30	4 4?	0 001
The threshold of angular deceleration, mean to the right and the left	control subjects	0 35	0.10		
The threshold of angular acceleration to the sid of the better ear	otoscl. patients	0 53	0.31	4 12	0 001
The threshold of angular acceleration, mean to the right and the left	control subjects	0 35	0 12		
The threshold of angular deceleration to the side of the better ea	otoscl patients	0.54	0 32	4 32	0 001
The threshold of angular deceleration mean to the right and the left	control subjects	0.35	0.10		

Table 21 *The mmed mplit des f the slow ph e f y t gmus when accelerating at a ate of on degree/sec² fr m a speed of 0°/sec to 60°/sec n the co trol serie a d in patient suff ring from toscle osis Th me n result e pr sed i degr e*

		MEAN	SD	T	P
Acceleration to the right	Control subjects	108	44	0 52	—
	Otoscler patients	101	67		
Acceleration to the left	Control subjects	108	38	1 43	—
	Otoscler patients	?1	64		

Table 2 *The m umm d mplit d f th slow phas of ny t gm s n g t f 1°/ f ng l a cele t fr m er t 60 d g / s in p t ent suffer g f m l n al t d ro o ly n on ear (17 p tient) M al p ss d in d g*

	Acceleration to the side of the affected ear	\ cel tion t th sid f the lin ally l ealthy e
MEAN	87	10
SD	58	61
MAX	10	70
MIN	?0	30

celerating to the left were 108 and 91 (table 21)

The summed amplitudes of the slow phase of nystagmus when using the angular acceleration of one degree/sec² from zero to 60 /sec in patients suffering from clinical otosclerosis in one ear only are lower in acceleration to the affected side (87) than in that to the clinic lly healtl y side (10?) The difference observed is not however tatistically significant The results are pre sented in table ?2

The mean summed amplitudes of the slow

phase of nystagmus when accelerating at a rate of one degree/sec² from zero to 60 /sec to the side of the more affected ear were 95 and to the side of the better ear 96 in patients suffering from otosclerosis In the control subjects the mean summed amplitude to the right was 108 which is precisely the same value as that obtained from the left side The difference is not statistically significant The results are presented in table 23

Table 23 *The mean summed amplitudes of the slow phase of nystagmus by staging rate of one degree/sec of angular acceleration from zero to 60°/sec to the side of the more affected ear and to the side of the better ear in patients suffering from otosclerosis (total 56 patients) and to the right and the left in the control subjects (total 40 accelerations) Mean values expressed in degrees*

Otoscler patients	Otoscler patients	Control subjects
Acceleration to the side of the more affected ear	Acceleration to the side of the better ear	Mean acceleration to the right and the lef
MEAN 95	96	108
SD 66	65	41
MAX 320	345	200
MIN 20	36	45

4 *Post otatory nystagmus*

When stopping abruptly from the speed of 60 /sec, the following mean summed amplitudes of the slow phase of the first post rotatory nystagmus in control series were manifested 119 right nystagmus beating and 117 left beating The corresponding mean values for patients suffering from otosclerosis were 120° and 118 (table 24) The maximum frequency for a period of ten seconds was correspondingly in control series 18,2 nystagmus beatings to the right and 19,2 to the left otosclerotic patients showed the values of 18,3 nystagmus beatings to the right and 18,6 beatings to the left Thus there were no statistically significant differences between the two sides or between the control series and the group of otosclerotic patients.

In patients suffering from unilateral otosclerosis (17 cases) the summed amplitude of the slow phase of the first postrotatory nystagmus after an abrupt stop from the speed of 60 /sec was 116° to the side of the affected ear and 1 1 to the side of the healthy ear

Correspondingly the mean summed amplitudes of the slow phase of the first post rotatory nystagmus were 108 to the side of the more affected ear and 116 to the side of the better ear in the whole group of patients suffering from otosclerosis (60 cases) The postrotatory nystagmus to the side of the more affected ear in both groups was weaker than that to the side of the better ear but no pronounced statistical significance could be established

D Comparison between audiological and electronystagmographical findings

The hearing of both ears at all frequencies studied was found to be worse in the patients who showed spontaneous or positional nystagmus in the electronystagmographic investigation (20 patients) than in those cases who showed *no nystagmus* in the above investigation (40 patients) In the higher frequency range the difference between the groups with nystagmus and with no nystagmus is greater though statistically significant differences were not demonstrated except in the left ear at 4 000 Hz in bone conduction ($p < 0{,}05$) and at 4 000 Hz and

Table 24 *The mean summed amplitudes of the slow phase of the first postrotatory nystagmus to the right and the left after an abrupt stop from the speed of 60°/sec. Comparison between control series and patients suffering from otosclerosis Mean values expressed in degrees.*

		MEAN	SD	T	P
The first postrotatory nystagmus to the right	Control subjects	119	60		
	Otoscl. patients	120	90	0 064	—
The first postrotatory nystagmus to the lef	Control subjects	117	60		
	Otoscl patients	118	96	0 036	—

Table 20 *C mparison between the m an thresholds of angular accele a i n a d d cel rati n to the side of the more aff cted ar and to th side f the better a in patients suffering f m tosel oss and the me n threshold of gular ac eleration and deceleration to the right and the left i co t ol bjects (expressed in d grees/sec²)*

		MEAN	SD	T	P
The threshold of angular acceleration to the side of the more affected ear	otoscl. patients	0.56	0.31	4 71	0 001
The threshold of angular acceleration mean to the right and the left	control subjects	0 35	0 1		
The threshold of angula deceleration to th sid of the more affected ear	otoscl patients	0.53	0.30	1 4	0 001
The threshold of angular deceleration, mean to the right and the left	control subjects	0 35	0 10		
The threshold of angular acceleration t the side of the better ear	otoscl. patients	0.53	0.31	4 12	0 001
The threshold of angular acceleration, mean to the right and the left	control subjects	0 35	0 1?		
The threshold of angular deceleration to the side of the better ear	otoscl. patients	0 54	0 32	4 3	0 001
The threshold f angular deceleration, mean to th right and the left	control subjects	0.35	0 10		

Tabl 21 *The summed amplitud s of the sl w phase of ystagm s u h n c lerat g t a rat f one degre /sec² from a spe d of 0°/sec t 60°/sec in th co t ol series and in patients ffern g f om otosclerosis Th mean esults pressed in degrees*

		MEAN	SD	T	P
Acceleration to the right	Control subjects	108	44	0 52	—
	Otoscler patients	101	67		
Acceleration to the left	Control subject	108	38	1 43	
	Otoscler patients	91	64		

Table 2? *Th m mmed mplit d f th low phas of ny t gmus using rat f 1°/ c ² of angula accele t fr m z t 60 d g e / sc in pat ent suffern g f om clinical t ler su only in on e (17 p t ent) Mea d p ess d d g*

	Acceleration to the sid of the affected ear	Acceleration t the sid of the clinically healthy ea
MEAN	87	102
SD	58	64
MAX	10	270
MIN	?0	30

celerating to the left were 108 and 91 (table 21)

The summed amplitudes of the slow phase of nystagmus when using the angular acceleration of one degree/sec from zero to 60 /sec in patients suffering from clinical otosclerosis in ne e r nly are lower in acceleration to the affected ide (87) than in that to the clinically healthy side (10?) The difference observed is not however statistically significant The results are presented in table 2?

The mean summed amplitudes of the slow

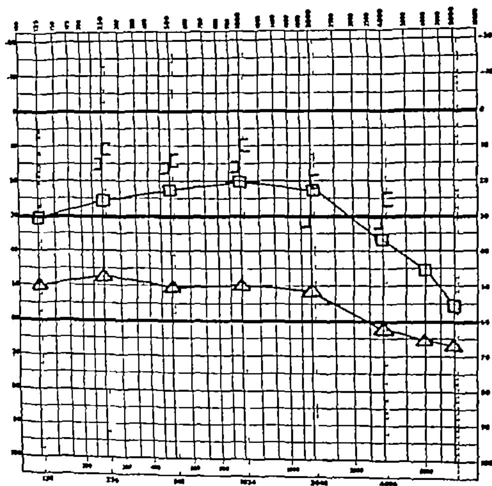


Fig. 4

The mean audiograms of the better and the worse ear in otosclerotic patients with recruitment
□ – better ear air conduction
Δ worse ear air conduction
ι better ear bone conduction
l worse ear bone conduction

Table 25. *The table shows the mean hearing loss in dB at various frequencies standard deviation, the t test value and any significance (p) in otosclerotic patients right and left ear separately. At each frequency the upper line represents the patients with manifested nystagmus (20 cases) while the lower line represents the patients where no nystagmus findings were established (40 cases)*

b.c.					
Hz		Hearing loss in dB MEAN	SD	T	P
1000 Right ear	Nystagmus in ENG No nystagmus in ENG	14 8 12.3	7 7 8.1	1 147	—
1000 Left ear	Nystagmus in ENG No nystagmus in ENG	17.5 13.5	7 7 8.4	1 783	—
2000 Right ear	Nystagmus in ENG No nystagmus in ENG	25.3 20.5	14 0 12.9	1.296	—
2000 Left ear	Nystagmus in ENG No nystagmus in ENG	30.3 23 6	15 9 1[illegible]4	1 775	—
4000 Right ear	Nystagmus in ENG No nystagmus in ENG	26.3 19.9	15 6 11 5	1 789	—
4000 Left ear	Nystagmus in ENG No nystagmus in ENG	29.3 21.5	13.3 12.4	2.276	0 05
a.c.					
4000 Right ear	Nystagmus in ENG No nystagmus in ENG	46.8 44.3	25.4 20.5	0.41	—
4000 Left ear	Nystagmus in ENG No nystagmus in ENG	62 7 47 8	19 0 19 1	2.88	0 01
6000 Right ear	Nystagmus in ENG No nystagmus in ENG	47 0 39 6	26.3 21 2	1 251	—
6000 Left ear	Nystagmus in ENG No nystagmus in ENG	58 3 42.4	22.1 23 6	2.505	0 01
8000 Right ear	 No nystagmus in ENG	51 5 43 8	28 0 23 5	1 129	—
8000 Left ear	 No nystagmus in ENG	60.7 48 3	22 7 28	1 817	—

6 000 Hz in air conduction (p < 0 01) The results are shown in table 25

Hypoexcitability on one side in the caloric tests was manifested in 25 patients. The hearing of this side was not statistically significantly lower than the hearing of the opposite side.

The occurrence of recruitment in proportion to nystagmus findings is shown in table 26 Positional nystagmus was discovered in all patients with recruitment The divergence is statistically highly significant (p < 0 001) The hearing results of these patients with recruitment are shown in table 27 and figure 4

Table 28 correspondingly shows the occurrence of subjective tinnitus in proportion to nystagmus findings Positional nystagmus was found to be of a significantly higher degree in the patients complaining of subjective tinnitus than in the other otosclerotic patients (p < 0 01) On the other hand patient who had vertigo or paracusis anamnestically did not show significantly more perceptible positional nystagmus than those lacking the symptoms mentioned There are no statistically significant differences between the

Table 26 *Recruitment and positional nystagmus of sclerotic patient*

	Recruitment N	No recruitment N
Nystagmus	7	13
No nystagmus	0	40

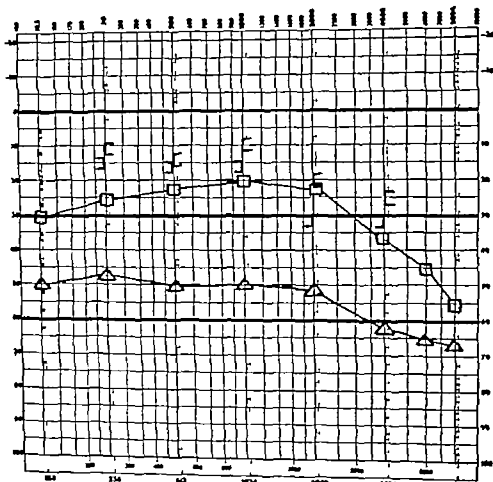


Fig 4

The mean audiogram of the better and the worse ear in otosclerotic patients with recruitment
☐ = better ear air conduction
Δ = worse ear air conduction
− = better ear bone conduction
| = worse ear bone conduction

Table 5. *The table sh[ows] th[e] me[an] hear[in]g loss i[n] dB [a]t [va]r[io]us f[re]qu[e]ncies standard d[ev]iati[on] th[e] t test val[u]e a[n]d any significance (p) in otosclerotic patients right a[n]d left [ear]s par[ate]ly [A]t each frequency the upper li[n]e represents the pat[i]ents [w]ith manifested nystagm[u]s (20 cases) whil[e] the l[ow]er line represents th[e] patients wher[e no n]y[sta]gm[u]s find[in]gs were est[a]blished (40 cases)*

Hz		Hearing loss in dB MEAN	SD	T	P
b.c.					
1000 Right ear	Nystagmus in ENG No nystagmus in ENG	14.8 12.3	7 7 8 1	1 147	—
1000 Left ear	Nystagmus in ENG No nystagmus in ENG	17.5 13.5	7 7 8.4	1 785	
2000 Right ear	Nystagmus in ENG No nystagmus in ENG	25.3 20.5	14 0 12.9	1 296	—
2000 Left ear	Nystagmus in ENG No nystagmus in ENG	30 3 23 6	13.9 1[illegible] 4	1 775	—
4000 Right ear	Nystagmus in ENG No nystagmus in ENG	26.3 19 9	13 6 11.5	1 789	—
4000 Left ear	Nystagmus in ENG No nystagmus in ENG	29.3 21.5	13 3 12.4	2.[illegible]26	0 05
a.c.					
4000 Right ear	Nystagmus in ENG No nystagmus in ENG	46.8 44.3	25 4 20 5	0 41	—
4000 Left ear	Nystagmus in ENG No nystagmus in ENG	62.7 47.8	19 0 19 1	88	0 01
6000 Right ear	Nystagmus in ENG No nystagmus in ENG	47 0 39 6	26.3 21 2	1 [illegible]51	
6000 Left ear	Nystagmus in ENG No nystagmus in ENG	58 3 42 4	22.1 23 6	2.505	0 01
8000 Right ear	No nystagmus in ENG	51.5 43 8	28 0 23 5	1 129	—
8000 Left ear	No nystagmus in ENG	60 7 48.3	22 7 28 2	1 817	—

6 000 Hz in air conduction ($p < 0.01$) The results are shown in table 25

Hypoexcitability on one side in the caloric tests was manifested in 25 patients. The hearing of this side was not statistically significantly lower than the hearing of the opposite side

The occurrence of recruitment in proportion to nystagmus findings is shown in table 26 Positional nystagmus was discovered in all patients with recruitment The divergence is statistically highly significant ($p < 0.001$) The hearing results of these patients with recruitment are shown in table 27 and figure 4

Table 28 correspondingly shows the occurrence of subjective tinnitus in proportion to nystagmus findings Positional nystagmus was found to be of a significantly higher degree in the patients complaining of subjective tinnitus than in the other otosclerotic patients ($p < 0.01$) On the other hand patients who had vertigo or paracusis anamnestically did not show significantly more perceptible positional nystagmus than those lacking the symptoms mentioned There are no statistically significant differences between the

Table 6 *R[ecr]ui[tmen]t and po[si]tio[n]al [n]y[sta]gm[us] [in] [o]t[osc]l[erotic] p[a]t[i]ent[s]*

	Recruitment No	No recruitment No
Nystagmus	7	13
No nystagmus	0	40

Table 27. Average hearing result of the better ear and the worse ear in otosclerotic patients with recruitment (7 patients. The values given are mean, standard deviation, maximum hearing loss, minimum hearing loss)

Hz		Better ear a.c.	Better ear b.c.	Worse ear a.c.	Worse ear b.c.
125	MEAN	30.7		50.0	
	SD	19.4		12.9	
	MAX	70.0		65.0	
	MIN	15.0		30.0	
250	MEAN	26.4	12.1	47.8	16.4
	SD	17.9	5.7	14.9	6.9
	MAX	65.0	20.0	65.0	30.0
	MIN	15.0	5.0	25.0	10.0
500	MEAN	23.6	14.3	51.4	17.1
	SD	18.6	6.7	15.7	8.0
	MAX	60.0	20.0	70.0	30.0
	MIN	5.0	5.0	25.0	10.0
1000	MEAN	20.7	10.7	30.7	17.1
	SD	15.6	4.5	21.3	9.3
	MAX	50.0	15.0	75.0	35.0
	MIN	5.0	5.0	15.0	5.0
2000	MEAN	22.1	20.7	52.8	32.8
	SD	16.5	9.7	24.3	18.2
	MAX	55.0	30.0	85.0	60.0
	MIN	5.0	5.0	20.0	10.0
4000	MEAN	37.9	25.0	62.1	32.8
	SD	15.2	13.2	13.5	11.1
	MAX	60.0	50.0	90.0	50.0
	MIN	25.0	10.0	50.0	20.0
6000	MEAN	46.4		65.0	
	SD	23.7		13.8	
	MAX	90.0		85.0	
	MIN	15.0		45.0	
8000	MEAN	56.4		67.1	
	SD	26.6		17.5	
	MAX	90.0		90.0	
	MIN	25.0		40.0	

Table 28. Subjective tinnitus and positional nystagmus in otosclerotic patients

	Tinnitus N	No tinnitus No
Nystagmus	11	9
No nystagmus	6	34

Table 29. Average hearing result of right and left ear in otosclerotic patients with anamnestic tinnitus (17 patients. The values given are mean, standard deviation, maximum hearing loss, minimum hearing loss)

Hz		Right ear a.c.	Right ear b.c.	Left ear a.c.	Left ear b.c.
125	MEAN	44.1		50.0	
	SD	20.5		16.5	
	MAX	70.0		75.0	
	MIN	10.0		30.0	
250	MEAN	42.6	13.9	49.4	14.7
	SD	22.1	7.2	17.0	7.0
	MAX	80.0	30.0	75.0	30.0
	MIN	5.0	5.0	25.0	5.0
500	MEAN	41.8	17.3	50.8	16.5
	SD	19.8	7.1	18.6	8.4
	MAX	70.0	25.0	90.0	30.0
	MIN	5.0	5.0	25.0	5.0
1000	MEAN	37.4	12.9	47.3	15.3
	SD	17.3	6.1	17.9	6.9
	MAX	60.0	25.0	75.0	35.0
	MIN	5.0	5.0	15.0	5.0
2000	MEAN	36.7	24.1	44.1	27.1
	SD	16.2	13.8	19.8	13.8
	MAX	60.0	60.0	80.0	25.0
	MIN	5.0	10.0	20.0	5.0
4000	MEAN	45.3	22.1	55.6	25.3
	SD	22.1	12.1	18.0	11.4
	MAX	90.0	50.0	85.0	50.0
	MIN	10.0	10.0	25.0	10.0
6000	MEAN	44.4		52.9	
	SD	23.4		21.9	
	MAX	90.0		85.0	
	MIN	15.0		15.0	
8000	MEAN	48.8		38.2	
	SD	22.5		21.4	
	MAX	90.0		90.0	
	MIN	15.0		20.0	

hearing of these patients with anamnestic tinnitus and with no anamnestic tinnitus. The hearing results are presented in table 29 and figure 5.

Twenty four patients had bone conduction values worse than 20 db (Mean of 250, 500, 1 000, 2 000, 4 000 Hz). Ten of these had also positional nystagmus in ENG investigation. The otosclerotic patients with sensorineural hearing loss had more vestibular disturbances than others. However this difference is not statistically significant.

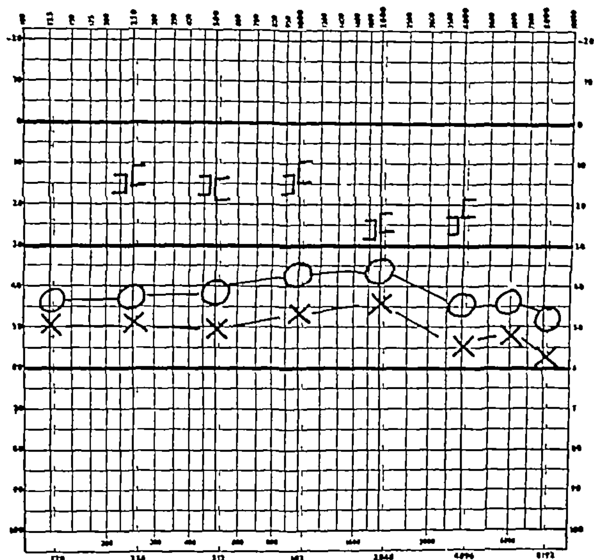


Fig 5

The mean audiogram of right and left ear in otosclerotic patient with ananmestic tinnitus
O = right ear air conduction
\ = left ear air conduction
[= right ear, bone conduction
] = left ear bone conduction

Table 27. *Average hearing results of the better ear and the worse ear in otosclerotic patients with recruitment (7 patients. The values given are mean, standard deviation, maximum hearing loss, minimum hearing loss)*

Hz		Better ear		Worse ear	
		a.c.	b.c.	a.c.	b.c.
125	MEAN	50 7		50 0	
	SD	19 4		12 9	
	MAX	70 0		65 0	
	MIN	15 0		30 0	
250	MEAN	26 4	12.1	47 8	16 4
	SD	17.9	5 7	14 9	6.9
	MAX	65 0	20 0	65 0	30 0
	MIN	15 0	5 0	25 0	10 0
500	MEAN	23 6	14 3	51 4	17 1
	SD	18 6	6 7	15 7	8 0
	MAX	60 0	20 0	70 0	30 0
	MIN	5 0	5 0	25 0	10 0
1000	MEAN	20 7	10 7	50 7	17 1
	SD	15 6	4 5	21 3	9 5
	MAX	,0 0	15 0	75 0	35 0
	MIN	5 0	5 0	15 0	5 0
2000	MEAN	22 1	20 7	52 8	32 8
	SD	16 5	9 7	24 3	18 2
	MAX	55 0	30 0	85 0	60 0
	MIN	5 0	5 0	20 0	10 0
4000	MEAN	37 9	25 0	62 1	32 8
	SD	13 2	13 2	13 5	11 1
	MAX	60 0	50 0	90 0	50 0
	MIN	25 0	10 0	50 0	20 0
6000	MEAN	46 4		63 0	
	SD	25 7		13 8	
	MAX	90 0		85 0	
	MIN	15 0		45 0	
8000	MEAN	56 4		67 1	
	SD	26 6		17 5	
	MAX	90 0		90 0	
	MIN	25 0		40 0	

Table 28. *Subjective tinnitus and positional nystagmus in otosclerotic patients*

	Tinnitus No	No tinnitus No
Nystagmus	11	9
No nystagmus	6	34

Table 29. *Average hearing results of right and left ear in otosclerotic patients with anamnestic tinnitus (17 patients. The values given as mean, standard deviation, maximum hearing loss, minimum hearing loss.)*

Hz		Right ear		Left ear	
		a.	b.c.	a.c.	b.c.
125	MEAN	44 1		50 0	
	SD	20 5		16 5	
	MAX	70 0		75 0	
	MIN	10 0		30 0	
250	MEAN	42 6	13 9	49 4	14 7
	SD	22 1	7.2	17.0	7.0
	MAX	80 0	30 0	75 0	30 0
	MIN	5 0	5 0	25 0	5 0
500	MEAN	41 8	17 3	50 8	16 5
	SD	19 8	7 1	18 6	8 4
	MAX	70 0	25 0	90 0	30 0
	MIN	5 0	5 0	25 0	5 0
1000	MEAN	37 4	12 9	47.3	15 3
	SD	17 3	6 1	17.9	6 9
	MAX	60 0	25 0	75 0	35 0
	MIN	5 0	5 0	15 0	5 0
2000	MEAN	36 7	24.1	44 1	27 1
	SD	16.2	13 8	19 8	13 8
	MAX	60 0	60 0	80 0	25 0
	MIN	5 0	10 0	20 0	5 0
4000	MEAN	45 3	22 1	55 6	25 3
	SD	22 1	12.1	18 0	11 4
	MAX	90 0	50 0	85 0	50 0
	MIN	10 0	10 0	25 0	10 0
6000	MEAN	44 4		52 9	
	SD	23.4		21 9	
	MAX	90 0		85 0	
	MIN	15 0		15 0	
8000	MEAN	48 8		58 2	
	SD	22.5		21 4	
	MAX	90 0		90 0	
	MIN	15 0		20 0	

hearing of these patients with anamnestic tinnitus and with no anamnestic tinnitus. The hearing results are presented in table 29 and figure 5

Twenty four patients had bone conduction values worse than 20 db (Mean of 250, 500 1 000, 2 000 4 000 Hz) Ten of these had also positional nystagmus in ENG investigation. The otosclerotic patients with sensorineural hearing loss had more vestibular disturbances than others However this difference is not statistically significant.

VI Discussion

In this investigation 34 patients (57 per cent) anamnestically complained of vertigo and unsteadiness while walking which is more than in any previous investigations. Only fourteen of these 34 patients showed nystagmus in ENG-investigation, however Nystagmus in ENG was observed in six further patients (who anamnestically revealed no vertigo or unsteadiness) Consequently ENG investigation does not always indicate nystagmus, despite anamnestic subjective vertigo Symptoms pointing to vestibular disturbances have been observed in otosclerotic patients by Rasmussen (1949) Hulk and Jongkees (1950) Aschan Bergstedt and Stahle (1956) Reinecken (1960) Fisch (1965) and Rüedi et al. (1965) Nevertheless comparatively sparse investigations on the pre-operative state have been published so far

Reinecken, for instance, has demonstrated positional nystagmus in 25 per cent and Fisch in 28 8 per cent of such patients Meurman et al. found positional nystagmus, directional preponderance or hypoexcitability in the caloric tests in 35.5 per cent of patients. *In this investigation positional nystagmus was verified in 20 patients (33,3 per cent)* which is approximately the same amount as in the previous investigations.

No positional nystagmus was demonstrated in the control series, but directional preponderance (a difference exceeding 20 per cent between the nystagmus values to the right and to the left) in the caloric tests was present in two subjects when measured from the maximum eye speed and in one when measured from total amplitude As calculated before, the patients suffering from otosclerosis revealed correspondingly directional preponderance in 29 and 32 cases These divergences between the control series and the patients suffering from otosclerosis were statistically significant ($p < 0\ 01$ and $p < 0\ 001$)

Unilateral hypoexcitability in the caloric tests (a difference exceeding 20 per cent between the two sides) was revealed in 34 patients (56.7 per cent) when measured from maximum eye speed and in 33 patients (55 per cent) when measured from summed amplitude The control series, on the other hand showed unilateral hypoexcitability in one subject only when measured from summed amplitude *The difference between the control group and the group of patients is highly significant ($p < 0,001$)*

The mean summed amplitudes of the slow phase of the nystagmus in the caloric tests did not statistically differ in patients suffering from otosclerosis and in control series.

Anamnestic tinnitus was demonstrated in 17 patients, and 11 of these (65 per cent) showed positional nystagmus in the ENG-investigation. These seventeen patients thus showed significantly more commonly nystagmus than the patients with no anamnestic tinnitus ($p < 0\ 01$) This observation has not been described in the literature.

Conductive hearing loss in otosclerosis is due to the fixation of the stapes in the oval window region Sensorineural hearing loss also occurs in association with otosclerosis. According to Shambaugh (1959) the cochlear damage is probably due to toxic secretions entering the endolymph. Active otosclerotic foci extending to the endosteum produce larger quantities of these substances injurious to the organ of Corti than does an inactive focus Fisch (1965) suggested that an otosclerotic vascular change or a biochemical change in the inner ear fluids might be the reason for cochlear and vestibular disturbances because the terminal fibres of nervus utriculari and nervi ampullares run freely in the perilymphatic space and can thus come into direct contact with the perilymph in association with biochemical changes caused by otosclerosis When examining the perilymph of otosclerotic patients Chládek and Opplt (1966) have described reduced alfa and beta globuline fraction in these patients Further Chládek and Opplt

(1968) established that there was a relationship between the range of the protein spectrum in the perilymph and the otosclerosis activity. Rüedi et al. (1965) observed higher calcium and protein values than normal in the perilymph of otosclerotic patients and also verified alkaline phosphatase, which does not normally exist in the human perilymph. However it appears that otosclerosis should not be a common cause of sensorineural hearing loss (Gross 1968). Schuknecht (1971) suggests that in general, otosclerosis probably has no effect on the cochlea of most patients. There are however severe cases of otosclerosis in which much of the otocapsule is involved, possibly with some lamellar new bone ingrowth where severe degenerative lesion brought about by otosclerosis definitely prevails. The patients with descending audiometric pattern, which most commonly appears in association with otosclerosis, would probably have had the same pattern even without otosclerosis, but on the other hand there is, according to Schuknecht, no pure cochlear otosclerosis without any stapes fixation. The average hearing loss of air conduction in this investigation was 50—60 dB in the more affected ear. The average hearing loss of bone conduction from 250 to 1 000 Hz was about 10—15 dB and from 2 000 to 4 000 Hz 20—25 dB. The sensorineural hearing loss was thus proved to be more pronounced for high tone. The control series did not show any pronounced hearing loss of the above kind. *The patients with objective vestibular disturbances also [illegible] more perspicuous sensorineural hearing loss than the others. This difference*, which is in agreement with Fisch (1965), *is statistically significant at 4 000 Hz in bone conduction (table 25).*

The recruitment phenomenon was previously assumed to be associated with peripheral, perceptive hearing loss only. It has been shown, however, that recruitment also occurs in association with pure conductive hearing loss, as with otosclerosis, for instance (Karja 1970). The phenomenon is presumed to be caused by the immobilization of the stapes and is probably a result of an altered stimulation pattern on the basilar membrane brought about by hydrodynamic changes in the cochlea (Andersson and Barr 1966).

Recruitment was found in seven patients (12 per cent) in this investigation, and all these patients showed objective vestibular disturbances as well.

In earlier investigations the thresholds of angular acceleration in normal subjects vary as shown by calculations made by Groen and Jongkees 0,5°/sec² (1948), Hilding 0,75—1,0°/sec² (1953), Montandon et al. 0,8°/sec² (1955) and Decher 0,4°/sec² (1965). These variations are caused at least partially by the different methods and apparata employed. In this investigation the acceleration was begun at the rate of 0,2°/sec² and after an acceleration of 90 seconds the rotation was kept constant for 120 seconds before the deceleration phase. The rates of acceleration and deceleration were always identical and they were heightened gradually by 0,2°/sec² at a time until the threshold was reached for both sides. Between every rotation there was a pause of 120 seconds for recovery. In this investigation the thresholds of acceleration in the control series were 0,37°/sec² to the right and 0,32°/sec² to the left, and correspondingly the thresholds of deceleration were 0,33°/sec² to the right and 0,37°/sec² to the left. Thus the threshold of acceleration to the right and the threshold of deceleration to the left were about identical and vice versa. The differences between the two sides are slight and have no statistical significance. The thresholds of control subjects are a little lower than in the previous investigations.

The threshold of acceleration was 0,49°/sec² to the right and 0,60/sec² to the left. The thresholds of deceleration were 0,58°/sec² to the right and 0,50°/sec² to the left. The differences in thresholds between the two sides are not statistically significant, but the thresholds of otosclerotic patients are statistically significantly higher than those of the control series (table 26).

In the 17 patients who had unilateral otosclerosis, the threshold of acceleration to the side of the affected ear was 0,68°/sec² and that to the side of the clinically healthy ear 0,54°/sec². The thresholds of deceleration are almost identical, 0,56°/sec² and 0,67°/sec². These differences are not statistically significant. The thresholds of acceleration show statistically significant differences between the control group and otosclerotic patients both for the more affected ear and for the clinically healthy ear ($p < 0,01$).

The thresholds of acceleration for the more affected ear and for the better ear in patients suffering from otosclerosis (60 patients) are approximately identical (0,56 °/sec² and 0,53 °/sec²). These two thresholds are, however, statistically very significantly higher than the thresholds of the control series in which the corresponding values are 0,35 °/sec² and 0,35 °/sec² (p <0,001).

When employing the rate of 1 °/sec² which is about 0,5 °/sec² higher than the average threshold during the acceleration phase there were no statistically significant differences in the summed amplitude of the slow phase of perrotatory nystagmus in the course of acceleration from zero to 60 °/sec between otosclerotic patients and the control series (table 21). Thus the elevated thresholds of angular acceleration and deceleration in otosclerotic patients might be presumed to be inflicted by changes in the perilymph of the labyrinth in association with otosclerosis.

Previous investigations have established that the first postrotatory nystagmus in otosclerotic patients is of shorter duration than in normal subjects (Rasmussen 1949, Hulk and Jongkees 1950). *In this investigation there was no statistically significant difference in the summed amplitude of the slow phase of the first postrotatory nystagmus between otosclerotic patients and the control series. No difference was demonstrated in the maximum frequencies of postrotatory nystagmus during the ten seconds control period either.*

Thus it can be concluded that the most commonly prevailing vestibular disturbances in patients suffering from otosclerosis are firstly caloric hypoexcitability and a heightened threshold of angular acceleration and deceleration, secondly directional preponderance and thirdly positional nystagmus in this order of frequency. All these abnormalities, as well as the sensorineural hearing loss, may be caused by the same factor connected with the otosclerotic focies in the labyrinthine capsule.

VII Summary

The aim of this study was to investigate the preoperative vestibular disturbances in patients suffering from otosclerosis. The material consisted of 60 patients suffering from otosclerosis and 20 control subjects. All patients and control subjects with any previous ear operation or head trauma were excluded. I addition to pure tone tests, speech audiometric tests and if possible loudness balance tests according to Fowler were also performed. The occurrence of spontaneous and positional nystagmus was investigated with ENG. The caloric tests were carried out according to Hallpike and in the rotatory tests Polman's rotatory chair was utilized (Mod. II e III).

In the ENG investigation 20 patients (33,3 per cent) revealed positional nystagmus. In f of them the nystagmus was direction-changing (Nylén's type I), in fourteen the nystagmus was found to be direction-determined (Nylén's type II) and in one patient the nystagmus type was irregular direction-changing (Nylén type III).

In the caloric tests directional preponderance was verified in 29 cases (48 per cent) when measured from the maximum eye speed and in 32 cases (53 per cent) when measured from the summed amplitude of the slow phase of nystagmus. Twenty-two patients 37 per cent) showed directional preponderance when calculated by the two methods jointly.

Caloric excitability was found to be reduced in 34 patients (57 per cent) (dif ference exceeding 20 per cent between the two sides) when measured from the maximum eye speed and in 33 cases (55 per cent) when measured from the summed amplitude of the slow phase of nystagmus. Twenty-five patients (42 per cent) revealed a lower caloric excitability when calculated by the two methods jointly.

Statistically significantly there are more numerous cases of directional preponderance and lowered caloric excitability in otosclerotic patients than in normal control subjects.

Patients with objective vestibular disturbances showed greater hearing losses at high frequencies than the others. The difference was statistically significant at 4 000 Hz in bone conduction and at 4 000 and 6 000 Hz in air conduction.

The mean thresholds of angular acceleration in otosclerotic patients were 0,49 °/sec² to the right and 0,60 °/sec² to the left. The corresponding values for deceleration thresholds were 0,58 °/sec² and 0,50 °/sec². These values are all statistically significantly higher than in the control group.

The mean threshold of angular acceleration in this group was to the right 0,37 °/sec² and to the left 0,32 °/sec². The values for deceleration were correspondingly 0 33 °/sec² and 0,37 °/sec².

Patients suffering from otosclerosis and the control series revealed no statistically significant difference when accelerating from zero t 60 °/sec at a rate of 1 °/sec² as measured from the summed amplitude of the slow phase of perrotatory nystagmus.

This investigation tends to demonstrate that patients suffering from otosclerosis very frequently show vestibular disturbances. The objective disturbances manifested were firstly caloric hypoexcitability and elevated thresholds of angular acceleration and deceleration, secondly directional preponderance and, thirdly positional nystagmus.

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SUPPLEMENT 307

Middle Ear Epithelium and Chronic Ear Disease

BY

PEKKA KARMA

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CONTENTS

1 INTRODUCTION AND PURPOSE OF THE STUDY

Chronic otitis media has been one of the most important subjects of otologic studies for over a hundred years. Research on middle ear histopathology was particularly lively late in the 19th and in the early decades of the 20th century the main subjects being the process of pneumatization and the etiology of cholesteatoma. Wittmaack published in 1918 his classical theory of pneumatization while von Troltsch (1868) Wendt (1873), Habermann (1888), Bezold (1888 1890), Politzer (1901), Wingrave (1910) Manasse (1917), Lange (1925) Nager (1925) Döderlein (1930) McKenzie (1931) and Albrecht (1931) were among the authors who discussed theories concerning the genesis of cholesteatoma.

Since World War II the use of the operating microscope has much increased the interest in ear surgery and in the changes thus observed. This, and new histological research methods, gave new impetus to the study of the histopathology of the middle ear Structural details of the middle ear mucosa were further clarified in the 1960s by the studies of Bendek (1963), Friedmann (1963) and Sadé (1965 1966 a) in particular Sadé (1965 1966 a) showed that the middle ear had a true mucosa with its secreting components and epithelial lining of a partly respiratory type During the last five years numerous histologic and cytologic studies based on light and electron microcopy as well as biochemical and microbiological studies of middle ear processes, have given us new and more extensive views on the nature of the tympanic mucosa.

One interesting recent finding was that specimens of middle ear mucosa, taken in connection with chronic ear surgery showed stratified squamous epithelium without cholesteatoma (T Palva et al., 1968) Although the removal of tympanic mucosa in these cases was not total, there was not a single case of cholesteatoma developing during the follow-up period of 4—5 years. The authors felt that two types of squamous epithelium exist, the "resting" hyperkeratotic, and that with slight or no keratinization with the general function of covering the epithelial defects of the tympanic mucosa. Only the hyperkeratotic would be capable of forming cholesteatoma. The removal of the small amount of keratin possibly connected with the non-hyperkeratotic type might be explained by horizontal epithelial migration (Litton, 1968), if a connection between the squamous epithelium and the ear canal could be shown.

The purpose of the present study was to examine systematically with the aid of serial sections, the type and characteristics of the epithelium in the chronically infected middle ear Special attention is devoted to the type of any squamous epithelium, its capacity for keratin formation, and its relationship to other epithelium. These findings will be compared with the tympanic pathology and related especially to the tympanic membrane pathology and to the epithelium of the perforation margins. The genesis of tympanic squamous epithelium is investigated, and an attempt is made to further elucidate the problem of epidermosis.

ciliated cylinder epithelium both in the tube and, in addition to flat single-layer epithelium, to a varying extent in the middle ear especially in its medial and lateral walls. No glands were found in the tympanum. They considered the tympanum a wide transitional region in which the entodermal respiratory epithelium of the tubal side changed into mesodermal pseudoendothelium. The same view of the embryonal development of the middle ear space was advocated by Marowitz & Porubsky (1971) who made their studies on rats.

Bendek (1963) on a material of ten otosclerotic ears, found secretory epithelium with glandular structures in three mucosal biopsies taken from the area of the fossa ovalis. This suggested that secretory epithelium was normally present on middle ear mucosa. Sadé (1965 1966 a) showed that the middle ear lining is a true mucosa containing secreting cells and glands (secretion) and covered very largely by ciliated epithelium (transmission). According to Sadé (1966 a) the ciliated epithelium extended from tube to tympanum in the form of tracts which lined the anterior tympanum, the hypotympanum and, to a lesser extent, the promontory and the anterior epitympanum. The cilia, on the whole, covered one to two anteroinferior thirds of the middle ear mucosa. In addition to pseudostratified columnar epithelium, cilia were borne e.g. on the promontory by cuboidal and even flat epithelial cells. Ten per cent of his autopsy material of 80 normal middle ears showed goblet cells in the neighbourhood of the orifice of the Eustachian tube whence they extended to the inferior tract, glands were seen beneath the ciliated epithelium in most ears.

Hentzer (1970) found that the ciliated epithelium in the middle ear region covered an even wider area than Sadé had claimed. He observed ciliated epithelium also in the area of the posterior tympanum, epitympanum, facial prominence and often even the mastoid air cells Furthermore, unlike Sadé (1966a) and Buch (1967), he noted high, and even pseudostratified ciliated epithelium on some areas of the tympanic surface of ear drum, however not in the area of the flat epithelium lining the pars flaccida (Hentzer 1969). Hentzer (1970) also reported gland like structures not only around the orifice of the Eustachian tube but also in the region of the promontory

Lim et al (1967) and Hussl & Lim (1969 a) studied with electron microscopy and Lim (1970) also autoradiographically the secretory structure and nature of the cells of the tympanic bulla in the guinea pig Kawabata & Paparella (1969) were the first to describe the normal ultrastructure of the epithelium of human promontory the promontory was lined by columnar or cuboidal, ciliated or non-ciliated cells, under which basal cells were visible on the basement membrane (= basal lamina). They found no goblet cells. Hussl & Lim (1969 b) and Lim & Hussl (1969) found that the respiratory epithelium of the human Eustachian tube became flattened in the tympanum until it was simple flat epithelium, the area of the *respiratory* epithelium approximately corresponding to the maximal extension reported by Sadé (1966 a) Additionally they saw in some places ciliated cells on the inner surface of the ear drum. The secretory cell types were goblet cells (especially in the neighbourhood of the tubal orifice) and intermediate cells (more tympanally in the area of the columnar cuboidal and also flat ciliated cells) which, according to the classification by Shackleford & Klapper (1962) belong to the seromucous and serous groups, respectively

2.2. MIDDLE EAR EPITHELIUM AND INFLAMMATION

According to Wittmaack (1918), the ciliated epithelium spread from the Eustachian tube to the tympanum only as a result of inflammation, and sometimes even extended to the air cell system. At the same time the

2 REVIEW OF THE LITERATURE

2.1 NORMAL MIDDLE EAR EPITHELIUM

According to Politzer (1878) and Preysing (1904) the middle ear was lined by ciliated epithelium over large areas that even extended to the epitympanum Preysing found *no glands on the tympanic mucosa* However von Tröltsch (1861) and Krause (1876) had already described glands in the middle ear mucosa, and the finding had been confirmed e g by Politzer (1878) and Goerke (1902 1905)

Wittmaack (1918) found ciliated epithelium only at the orifice of the Eustachian tube and over a small area of the floor of the anterior tympanum Otherwise there was simple cuboidal epithelium, with flat endothelium like areas He saw no glands in the normal tympanum Wittmaack's (1918) idea of one normal type of mucous membrane and of three pathological mucosal constitutions, was supported e.g by Steurer (1926) Alexander (1927) on the other hand asserted that all of Wittmaack's four mucosal types could be present in the same normal middle ear and the presence of ciliated epithelium in the antrum on the surface of the hyperplastic type of mucosa was only another sign of normal variation Meyer (1931) described in the tympanum all epithelial types from endothelium to the ciliated columnar epithelium producing mucus The thickness of the submucosa varied accordingly flat epithelium corresponding to thin submucosa. He was of the opinion that epithelium held the dominating role and that the submucosa (and the pneumatization of the mastoid process) were determined by the epithelial potency

According to Doderlein (1920) the ectodermal tympanal epithelium was low and cuboidal excepting the *ciliated columnar epithelium* of the tubal region Stewart (1928) shared Krainz's (1924) opinion that tympanic epithelium was of entodermal pharyngotubal origin flattening peripherally with cilia ending *in the anterior tympanum* close to the tube.

Up to the 1960s middle ear epithelium was generally believed to be low cuboidal non-ciliated unstratified and/or even endothelium like (Beck 1926 Rüedi 1937 1940 Lierle & Potter 1941 Friedmann 1955 b 1956) Only in the neighbourhood of the orifice of the Eustachian tube was it higher possibly stratifield and/or ciliated (Semenov 1936 Polvogt & Babb 1940 Maximov & Bloom 1942 Friedmann 1963) Ojala (1950) concurred with the idea of flat tympanal epithelium but showed that in pouch formations on top of a thicker subepithelial tissue layer and in the lateral wall of the hypotympanic recess, the epithelium was higher cuboidal or low columnar None of these authors found mucus secreting cells or glandular structures in the normal middle ear

In contrast to Hammar's (1902) generally accepted view that the middle ear lining was of entodermal origin Schwarzbart (1958 1959) asserted that the entodermal mucosa extended only to the isthmus of the Eustachian tube and that the bony tube (protympanum) as well as other middle ear spaces were lined with unciliated mesothelium He believed that the glandular structures were accordingly confined to the region of the cartilaginous tube (cf Tos, 1970) Buch & Jorgensen (1964) in their material of 135 ears of prematures in the 6th to 9th foetal month, found stratified

ciliated cylinder epithelium both in the tube and, in addition to flat single-layer epithelium, to a varying extent in the middle ear especially in its medial and lateral walls. No glands were found in the tympanum. They considered the tympanum a wide transitional region in which the entodermal respiratory epithelium of the tubal side changed into mesodermal pseudoendothelium. The same view of the embryonal development of the middle ear space was advocated by Marowitz & Porubsky (1971) who made their studies on rats.

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be an abrupt transition from one type of epithelium to the other and in some cases Sadé found simultaneously mucus forming and keratin-forming cells even in the same population of epithelial cells. He thought that the germinal cells of the epithelium possessed a capacity of differentiation into various directions, the results of which depended on local microenvironmental inductors.

In enzymologic studies these two types of squamous epithelium (T Palva et al., 1970 a) did not show remarkable qualitative differences, although in the cholesteatomatous type the epithelial enzyme activity usually was more pronounced. Only non-specific esterase behaved reversely whereas large subepithelial cholinesterase accumulations were seen in the active cholesteatoma of children (T Palva et al., 1971). Additional enzymological elucidation of squamous epithelium and the process of cholesteatoma has been sought e.g by Walsh (1953), Harris (1962), Paparella & Dito (1964) Jarrett & Spearman (1967) Maeda et al. (1967), Abramson (1969) T Palva et al (1970 b), Paparella et al (1970) Abramson & Gross (1971) and T Palva et al. (in press). So far however no enzymological explanation has been found for the epithelial changes in connection with middle ear inflammation. The most remarkable enzymologic finding to date is perhaps that by Abramson (1969) and Abramson & Gross (1971), viz. the pronounced collagenase activity of the cholesteatoma membrane (epithelium plus mesenchyma), which confirms the opinion (Lautenschlager 1927 McKenzie, 1931 Walsh, 1951 1953 Harris, 1962) that the cholesteatoma has a capacity for lytic expansion

2 3 CHOLESTEATOMA (EPIDERMOSIS) AND ITS ETIOLOGY

Cholesteatoma, or epidermosis (Tumarkin, 1958 1961) refers to the expansive process formed by the hyperkeratotic squamous epithelium and the underlying connective tissue. Despite assiduous research and numerous theories, the etiology of cholesteatoma is still an unresolved question. Full unanimity has not even been reached as to whether cholesteatoma is the cause or result of an inflammation (see McGuckin, 1962)

2.3 1 *The epidermoid theory (congenital cell inclusions)*

Cholesteatoma has been ascribed by many to congenital epithelial cell inclusions in the areas concerned (e.g. Körner 1899 McKenzie, 1931 Teed, 1936 Diamant, 1937 1948, 1952 1953). This theory has today been practically replaced by the assumption of an acquired etiology Primary congenital cholesteatoma does occur but only rarely in the middle ear spaces (Eggston & Wolff 1947) Case reports have been published e.g. by Lucae (1873) Kuhn (1891), Schwartze (1896) Erdheim (1905) Grove (1929), Lindsay (1934), M D Friedman & Quittner (1938), Holmes (1938), Cawthorne & Griffith (1961), Cawthorne (1963) Derlacki & Clemis (1965) Derlacki, Harrison & Clemis (1968) and Kärja & Laine (1970).

2.3.2. *The traumatic theory*

Through surgical or other trauma, epidermal material may be immigrated or implanted into middle ear spaces (e.g. Thulin, 1947 Nilsson, 1948 Kelemen, 1950 Escher 1954 Schröer 1958; Beichert, 1958 Seiferth, 1961) Traumatic etiology is generally accepted, although it explains only a fraction of the cases of cholesteatoma.

2.3.3 *The metaplastic theory*

2.3.3 1 Suppuration

According to Wendt (1873) chronic inflammation could cause squamous metaplasia of the middle ear epithelium, leading even

epithelial cells to a varying extent were transformed into goblet cells and gland like formations were also seen. In acute and chronic infection according to Wittmaack, *the extent and degree of these epithelial* changes, and the tympanal histopathology in general varied according to the type of in fection Döderlein (1920) found that in in flammation epithelial cells became oedematous and higher but the ciliated epithelium was always confined to the neighbourhood of the tubal orifice. He also noted cysts and as a result of an organization process, pseudocysts in the mucosa No true glands were seen even in a pathological tympanum Beck (1926) and Singer (1933) considered that tympanic epithelium may start secreting mucus in inflammation According to Ojala (1950) trophic stimulus resulting from in flammation produces hypertrophy of tym panic epithelium and the flat epithelium changes into ciliated columnar epithelium. Inflammation can also sometimes cause the epithelium to proliferate and produce gland like formations, in addition to the simpler secretory function

Friedmann (1955 a, b) produced an arti ficial infection in the tympanic bulla of the guinea pig and found that normal flat endothelium like epithelium was reverted to columnar epithelium of the respiratory type even containing goblet cells and gland like structures, within no more than a fortnight. In human material similar epithelial changes were noted (*Friedmann, 1956 T Palva* et al., 1964) in the mucosa of biopsies taken in connection with mastoidectomy Senturia et al (1962) cauterized the Eustachian tube in dogs and found, in about six months, glands lined by respiratory (columnar ciliated) epi thelium The glands were still noticeable after one year (Carr Ahlvin & Senturia 1967) Senturia et al (1962) observed no metaplasia to squamous epithelium and *Senturia (1963)* assumed that whatever tympanic squamous epithelium there was had immigrated

Zechner (1965 1966) and Zechner et al. (1968) found epithelial hyperplasia and meta plasia in chronic middle ear inflammation The metaplasia was either respiratory or *squamous* epithelial metaplasia, and both types of transformation could be seen vary ingly in the same middle ear Metaplastic squamous epithelium failed to keratinize and could be located side-by-side with columnar epithelium without any cellular or connective tissue reaction, whereas immigrating kera tinizing squamous epithelium pushed the middle ear epithelium forward, growing un derneath or sometimes over it. Zechner (1965 *1966)* also mentioned the mucosal gland like structures retention cysts and in the area of squamous epithelium intraepithelial cysts.

According to Sadé (1966 b) the middle ear mucosa in secretory otitis reacts by means of hyperplastic transformation and e.g hy peractive mucous glands are formed. Similar secretory hyperplasia was seen by Sadé & Weinberg (1967 1969) in specimens taken from chronic middle ear processes

In the study of T *Palva* et al *(1968)* referred to in the Introduction the authors assumed that, in the chronically infected tympanum two types of squamous epi thelium may appear different in clinical behaviour but except for the amount of keratin indistinguishable in histological structure The main function of non-cholesteatomatous squamous epithelium would be to line the denuded middle ear surfaces. *The resting squamous* epithelium on the other hand is hyperkeratotic and cholestea toma forming

In 60 of a total of 100 biopsies taken from chronically infected middle ear cleft mucosa, Sadé & Weinberg (1969) also found squamous epithelial metaplasia" which in 42 cases was *keratinizing Sadé (1971)* agreed that the squamous epithelium in chronic otitis was either a type that keratinized poorly or one that was hyperkeratotic, cholesteatomatous. *The same* ear could also show a change into mucus producing cells. There could

be an abrupt transition from one type of epithelium to the other and in some cases Sadé found simultaneously mucus forming and keratin-forming cells even in the same population of epithelial cells. He thought that the germinal cells of the epithelium possessed a capacity of differentiation into various directions, the results of which depended on local microenvironmental inductors.

In enzymologic studies these two types of squamous epithelium (T Palva et al., 1970 a) did not show remarkable qualitative differences, although in the cholesteatomatous type the epithelial enzyme activity usually was more pronounced. Only non-specific esterase behaved reversely whereas large subepithelial cholinesterase accumulations were seen in the active cholesteatoma of children (T Palva et al., 1971) Additional enzymological elucidation of squamous epithelium and the process of cholesteatoma has been sought e.g. by Walsh (1953), Harris (1962), Paparella & Dito (1964), Jarrett & Spearman (1967) Maeda et al. (1967), Abramson (1969), T Palva et al. (1970 b), Paparella et al. (1970) Abramson & Gross (1971) and T Palva et al. (in press) So far however no enzymological explanation has been found for the epithelial changes in connection with middle ear inflammation. The most remarkable enzymologic finding to date is perhaps that by Abramson (1969) and Abramson & Gross (1971) viz. the pronounced collagenase activity of the cholesteatoma membrane (epithelium plus mesenchyma), which confirms the opinion (Lautenschläger 1927; McKenzie, 1931 Walsh, 1951 1953 Harris, 1962) that the cholesteatoma has a capacity for lytic expansion.

3 CHOLESTEATOMA (EPIDERMOSIS) AND ITS ETIOLOGY

Cholesteatoma, or epidermosis (Tumarkin, 1958 1961), refers to the expansive process formed by the hyperkeratotic squamous epithelium and the underlying connective tissue. Despite assiduous research and numerous theories, the etiology of cholesteatoma is still an unresolved question. Full unanimity has not even been reached as to whether cholesteatoma is the cause or result of an inflammation (see McGuckin, 1962)

2.3 1 *The epidermoid theory (congenital cell inclusions)*

Cholesteatoma has been ascribed by many to congenital epithelial cell inclusions in the areas concerned (e.g. Körner 1899 McKenzie, 1931 Teed, 1936 Diamant, 1937 1948 1952, 1953) This theory has today been practically replaced by the assumption of an acquired etiology Primary congenital cholesteatoma does occur but only rarely in the middle ear spaces (Eggston & Wolff 1947) Case reports have been published e.g. by Lucae (1873), Kuhn (1891), Schwartze (1896) Erdheim (1905), Grove (1929) Lindsay (1934), M. D Friedman & Quittner (1938) Holmes (1938) Cawthorne & Griffith (1961), Cawthorne (1963) Derlacki & Clemis (1965), Derlacki, Harrison & Clemis (1968) and Kärja & Laine (1970)

2.3.2. *The traumatic theory*

Through surgical or other trauma, epidermal material may be immigrated or implanted into middle ear spaces (e.g. Thulin, 1947 Nilsson, 1948 Kelemen, 1950 Escher 1954 Schroer 1958 Beichert, 1958 Seiferth, 1961) Traumatic etiology is generally accepted, although it explains only a fraction of the cases of cholesteatoma.

2.3.3 *The metaplastic theory*

2.3.3 1 Suppuration

According to Wendt (1873) chronic inflammation could cause squamous metaplasia of the middle ear epithelium, leading even

to keratinization and cholesteatoma. Although squamous epithelial metaplasia is a generally accepted and verified phenomenon histologically this kind of cholesteatoma genesis has not been possible to verify as yet. However several reports have been published even recently on metaplastic squamous epithelium found in a chronically infected middle ear (Bendek, 1963 Zechner 1965 1966 Sadé & Weinberg 1969 Sadé 1971) and some has been found to be of a keratinizing type (Bendek 1963 Sadé & Weinberg 1969 Sadé, 1971) Sadé (1971) advocates the metaplastic etiological mechanism of cholesteatoma but admits that more than one etiology is possible.

2.3.3.2 Desiccation

Wingrave (1910) found that air entering the antro-tympanum through tympanic membrane perforation reduces the temperature and humidity of the middle ear space with *the result that the mucous membranes are* desiccated If the desiccation continues long enough it stimulates the epithelium towards transformation into squamous epithelium and the final result of the process is cholesteatoma. This theory has not found supporters as it presupposes that the cholesteatoma does not develop until inflammation has ceased and the ear with a large permanent perforation of the drum membrane has become dry

2 3 4 *The immigration theories*

A common feature is the supposition that cholesteatoma will not develop unless the stratified squamous epithelium of the drum membrane or of the adjacent ear canal immigrates into the middle ear space. The immigration theory with its modifications, is the most widespread and accepted theory of the genesis of cholesteatoma.

Habermann and Bezold in 1888 (cited by Portman, 1963) said that acute necrotizing otitis provoked immigration of the ear canal epithelium through epitympanic perforation. Bezold (1890) considered that the basic cause was the occlusion of the Eustachian tube which produced an invagination and rupture of Shrapnell s membrane and an immigration of epidermis into the epitympanum followed by the formation of cholesteatoma According to Wittmaack (1926) this cholesteatoma presupposed hyperplasia of the middle ear mucosa due to asymptomatic neonatal otitis and invagination and the possible rupture of the ear drum caused by the resulting low pressure Consequently cholesteatoma could expand without perforation, merely by means of a 'biological factor stimulating epidermal growth Furthermore a number of the cholesteatomata developed secondarily after necrotizing otitis (and the resulting total defect of the drum) Views in agreement with those of Wittmaack have later been advanced e g by Almour (1930) Day (1941) Jordan (1963) and Juers (1965) According *to them however the invagination had to* cause a rupture if a (primary acquired) cholesteatoma were to be formed Also Day *(1934 1941) Jordan (1963) and Juers (1965)* emphasized the role of humidity in stimulating desquamation and in causing and accelerating the growth of cholesteatoma.

Politzer (1901) already pointed out the considerable growth tendency of the epidermis of Shrapnell s membrane and the epidermis of the nearby ear canal (also Manasse, 1917) as a condition for the genesis of acquired cholesteatoma Nager (1925) Hellman (1925) and Lange (1925 1932) claimed that the basal cell layers of the epidermis of Shrapnell s membrane proliferated owing to chronic irritation The developing epidermal projections invaded the submucosa of Prussak s space (Lange) in the middle ear thus forming a "basis of cholesteatoma Similar changes were described by Steurer (1929 1950) Albrecht (1931 1950) and Schwarz (1932) Albrecht & Schwarz (1933) emphasized the role of the epitympanic connective tissue rests in the formation of

Shrapnell's cholesteatoma the process could be triggered off e.g. by a simple eczema of the ear canal (Steurer 1929 Albrecht, 1950), or a tubal catarrh (Steurer 1929 Schwarz, 1962).

When the ear canal or middle ear was experimentally irritated by various chemical agents (Berberich, 1927 Hoshiya, 1935 Schröer 1957) it was found that the epidermis of the ear canal proliferated and grew through a paracentetic hole or spontaneous perforation, into the middle ear forming cholesteatoma. Friedmann (1955 a, b) infected the tympanic bulla of guinea pigs and found that keratinizing squamous epithelium migrated through the perforated tympanic membrane and formed a cholesteatoma. Rüedi (1959), with a mixture of talc and fibrin, provoked an experimental foreign body reaction in the middle ear of guinea pigs with intact ear drums. He saw acanthosis and hyperkeratosis in ear drum epidermis which immigrated to form a cholesteatoma behind the intact tympanic membrane.

Rüedi (1957 1958 1959 1963 1965) stated that all acquired middle ear cholesteatomata developed as a result of an immigration of the epidermis of the ear canal or the drum, regardless of whether the tympanic membrane was intact or not. Predisposing factors were the elevated growth potential (in early childhood) of the skin of the superior ear canal close to the tympanum, and the submucosal connective tissue in the middle ear spaces resulting from incomplete pneumatization. Neither Friedman (1955 b) nor Rüedi (1958) observed in their experimental studies any sign of squamous epithelial metaplasia or cholesterol granuloma in the guinea pig bulla. According to Ojala & Saxén (1952) the connective tissue layer of the normal Shrapnell's membrane inhibits immigration. For a cholesteatoma to develop it is therefore necessary that the normal correlation between epidermis and corium should have been destroyed by an inflammatory process. Immigration and genesis of cholesteatoma could then take place through openings in the corium of imperforated pars flaccida or one perforated during inflammation. The prerequisite of cholesteatoma in both cases is the type of the mucosa it must be hyperplastic. If the mucosa is too fibrous (cicatricial), the epidermis cannot grow into it. Thus the cases with "inferior" mucosal constitution and recurrent otitic processes in childhood are particularly prone to cholesteatoma formation.

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of myelin sheaths, was used. According to the method developed by Pearse (1954), the staining was effected with the Luxol Fast Blue solution, using lithium carbonate for differentiation and warm cresyl echt violet solution for counterstaining.

This method gave the phospholipids a turquoise colour

Baker' acid hematin staining

Baker (1946) modified the Smith-Dietrich method (Dietrich 1910) to increase its specificity to phospholipids Under this method, after potassium bichromate-calcium chloride treatment, the sections were stained with Baker' acid hematin solution The sections were then washed, and differentiation took place in borax potassium ferricyanide solution. No prefixative phospholipid extraction was carried out.

The underlying principle of this method is that phospholipids are easily bound with chromium salts into insoluble compounds which, with acid hematin, stain blue black to black.

Ladewig modification f Mallory' staining

The sections were first stained with Weigert' haematoxylin solution, washed with water and placed in 5 per cent phosphotungstic acid solution for 1—3 minutes (until the connective tissue showed pink rose colour) They were then re-washed with water and placed for 2 minutes into Ladewig's staining solution [Composition /s g water-soluble aniline blue + 2 g Orange G + 8 cc glacial acetic acid + 100 cc distilled water The mixture is boiled, filtered and cooled, 1 g acid fuchsin (Rubin S) is added, and filtered] After this the sections were quickly rinsed in water and placed directly into 95 per cent alcohol, where they were differentiated until all excessive aniline blue came off

In addition to the characteristics typical of the normal Mallory' staining, this modification gives a reddish-violet colour to keratin and keratohyalin granules in the squamous epithelium. This is apparently because the keratin disulphide groups and the sulphhydryl groups of the immature keratin have better affinity to Ladewig modification.

Ayoub-Shklar's modification f Mallory staining

Ayoub & Shklar (1963) developed method based on Mallory' connective tissue staining, to stain keratin and pre-keratin. This method for formalin-fixed specimens omits the Mallory stages with the alcoholic iodine solution and the sodium thiosulphate solution necessary for Zenker-fixed specimens. The acid fuchsin solution used had ten times higher concentration than in Mallory' method. According to Ayoub & Shklar, this method stains keratin brilliant red and the epithelium purple gray. Stratum spinosum also sometimes shows areas of orange staining suggesting pre-keratin.

These keratin stainings were used in order to stain specifically epithelial phospholipids, keratin (and pre keratin), and in this way to obtain information on the type and degree of keratinization of tympanic squamous epithelium.

3 MATERIAL AND TECHNIQUES

3 1 MATERIAL

The material comprised 13 chronically in flamed middle ears. It was collected from September 1967 to March 1969 by daily examination of the ears of the deceased un dergoing autopsy at the Department of Pathology University of Oulu. All temporal bones with signs of chronic middle ear processes were removed The cadavers had been in cold storage for 13—91 (mean 58) hours before the autopsy

3 2 TECHNIQUES

3.2.1 *Preparation of sections*

The removed temporal bones were fixed in phosphate-buffered 10 % formalin solution where they remained for 1—9 months. The fixation fluid was changed at 2—3 month intervals.

Before decalcification the removed temporal bones were trimmed with a saw so that the first sawing line passed to the side of the ear drum cutting the ear canal close to the tympanum, and the second sawing line medially of the pars petrosa of the temporal bone leaving the whole middle ear in the block. The other sawing directions intersected the former transversely so that the tympanic half of the Eustachian tube was included, and on the mastoid side the preparation was cut at the level of the vertical part of the facial canal.

The decalcification took place in 22.5 % formic acid sodium citrate solution which was changed twice weekly The period of decalcification, depend g on the hardness of the block, ranged from 6 to 8 weeks.

The celloidin-paraffin double embedding method was used. The middl ear blocks were sectioned w th rotary microtome (Leitz Wetzlar) ertically so that the cutting line ra frontally corresponding to a lin from the ear drum towards the promontory The section always started at the orifice of the Eustachian tube and continued posteriorly to the vertical part of the facial canal. The order of sectioning and staining was the following

1 3 sections, 10 μ thick, were stained with Haematoxylin-Eosin (H E)
2. 2 sections, 25 μ thick, were discarded
3 3 sections, 10 μ thick, were used for mucus and keratin stainings
4 3 sections, 10 μ thick, were stored for later staining
5 2 sections, 25 μ thick, were discarded
1 3 sections, 10 μ thick, were stained with H E, and so on, in the same order as above

3.2.2 *Staining methods*

3.2.2.1 Routine staining

Haematoxylin-Eosin (H E) staining (Harris)
The systematic study and analysis of the middle ear mucosa was made from sections stained with haematoxylin-eosin. In this way the structure of the middle ear at 160 μ intervals, was investigated.

3.2.2.2 Mucus stainings

Periodic Acid Schiff (PAS) staining according to the MacManus method
According to Leblond et al. (1957) PAS-positi reaction in paraffin sections after the removal of glycogen is obtained only from the carbohydrate-protein complexes. However the method of staining used did not include a diastase digestion, and therefore the polysaccharides also ga e a PAS-posit e reaction (Magenta).

Alcian Blue (AB) staining
The sections were stained in Alcian Blue 7 G solution (30 minutes) and cou terstained with Kernechtrot solution (5 minutes). The method used did ot include a hyaluronidase phase This method, together w th the PAS staining was used mainly to study the ep thelial secretory function.

3 2 2 3 Keratin stainings

Al er C pper Phthalocyanine stain g
A copper phthalocyanine compound de loped by Al er & Barrera (1953 1954) c lled Luxol Fast Blue (Dupont) originally intended for the stain ng



Fig. 1. General view of the tympanum. (MAE = meatus ac. ext. T = tympanum, P = perforation edge.) H—E.



Fig. 2. 0.2 mm posteriorly to the level of Fig. 1. The upper margin of the perforation. The squamous epithelium of the ear canal side loses its stratum granulosum a few tenths of a millimetre before the tip (arrow), and continues over the edge for a short distance onto the tympanal side. H—E 40 x.



Fig. 3. A closer view of the perforation edge in Fig. 2. On the tympanal side the squamous epithelium becomes thinner and is changed into metaplastic epithelium (arrow) some 0.2 mm beyond the edge. H—E 160.

4 CASE REPORTS AND HISTOLOGICAL FINDINGS

This chapter gives a detailed description of all the 13 middle ears examined by serial sections and various staining methods. Altogether about 8000 sections were examined and special attention was paid to the characteristics of the middle ear epithelium.

The squamous epithelium seen in the tympanum is classified as immigrating or metaplastic (see Discussion) The immigrating type refers to squamous epithelium which is in continuity with the ear canal epidermis. The metaplastic type refers to squamous epithelium that is independent, without connection or junctional with connection to the immigrating squamous epithelium The change of normal epithelial type seen in a certain place in the middle ear is called metaplasia even if the change is too slight to permit the determination of this final type.

4 1 TEMPORAL BONE 1

The patient had died of coronary thrombosis at the age of 85 years He had been deaf for many years, but no other otologic history was available. Otoscopy revealed profuse discharge and an extensive central perforation of the pars tensa in the left ear

4 1 1 *Histology*

The central perforation of the pars tensa had a diameter of about 5 mm (Fig 1) The remaining parts of the drum membrane were 0.2—0.3 mm thick. The squamous epithelium of the ear canal grew over the lower edge of the perforation and after an abrupt junction at the edge continued onto the tympanic side of the drum for 0.3—0 4 mm as thin metaplastic squamous epithelium (Figs 4 5) Metaplasia then became weaker and the epithelium continued resembling a 2—3 layered cuboidal epithelium to the lower posterior part of the tympanum where it gradually changed into typical cuboidal epithelium In the anterior lower parts of the tympanum, the squamous epithelium underwent an abrupt change into slightly metaplastic cuboidal and at a distance of 0.5 mm, ciliated columnar epithelium (Fig 6) In the upper margin of the perforation the squamous epithelium of the ear canal crossed over into the tympanic side for 0 1—0 2 mm (Figs 2 3) Immediately before the perforation edge the squamous epithelium lost its stratum granulosum, and after a short intermediate phase as squamous epithelium on the tympanic side of the drum, it continued as metaplastic cuboidal and low columnar epithelium

The incus was absent and all that remained of the malleus was its head with a bony



Fig 1 General view of the tympanum (MAE = meatus ac. ext., T = tympanum, P = perforation edge) H—E.

Fig 2 0 2 mm posteriorly to the level of Fig 1. The upper margin of the perforation The squamous epithelium of the ear canal side loses its stratum granulosum few tenths of millimetre before the p (arrow), and continues over he edge for short di tance onto the tympanal side H—E 40



Fig 3 A closer view of the perforation edge in Fig. 2 On the tympanal side the squamous epithelium becomes thinner and is changed into metaplastic epithelium (arrow) some 0 2 mm beyond the edge H—E 160 x.



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Fig. 6. 0.6 mm anteriorly to the Fig. 1 level. The squamous epithelium (SQ) immigrates at the lower perforation margin onto the tympanic side and is changed, in the lower lateral area of the tympanum, over a short (0.3 mm) metaplastic zone (M) into ciliated columnar epithelium (R). H—E 160 x.

Fig. 7. Low columnar epithelium, with identifiable cilia, from the upper lateral part of the posterior tympanum. A secretory film is seen on top of the ciliary layer. H—E 400.





Fig 4 0.[illegible] mm posteriorly to the level of Fig 1 The lower margin of the perforation On the perforation edge the epidermis is changed into thin metaplastic epithelium (arrow). H—E 40 x.

Fig 5 A closer view of the lower perforation edge Fig 4 About 0.2 mm before the junction, the epidermis loses the stratum granulosum (arrow) and continues to the junction as a parakeratotic type. Prickles were seen up to the junction line H—E 160 x.



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Fig. 7. Low columnar epithelium, with verifiable cilia, from the upper lateral part of the posterior tympanum. A secretory film is seen on top of the ciliary layer. H—E 400 x.



union to the roof of the epitympanum The cariotic stapes was surrounded by fibrous tissue.

The promontorial epithelium was cuboidal with 1—3 layers, and in some areas it even changed into flat endothelium like lining In the posterior part of the middle ear the epithelium was highest at the floor where some of the epithelium had undergone a mucous change. Hardly any secretory cells were seen in the tympanum. The tympanic mucosa was thick and oedematous Only in the medial wall was it somewhat fibrotic.

The anterior tympanum showed not only cuboidal and low columnar epithelium but also especially in the roof and in the lower parts, metaplastic type epithelium (the epithelium was multilayered the epithelial cells and nuclei were disorganized cytoplasm had shrunk, and cellular eosinophilia had increased in H E staining) Backwards the metaplasia disappeared, and was only seen in the neighbourhood of the perforation edges and over a small area in the upper medial wall of the posterior tympanum At the orifice of the Eustachian tube, the epithelium was largely of the respiratory type A strip of ciliated cells continued from the tube posteriorly in the lower and upper lateral parts of the middle ear to the posterior tympanum (Fig 7) Also, a small strip of ciliated cells was seen on the luminal roof to the level of the posterior part of the promontory

Keratin stainings of the tympanic epithelium were negative The minute keratin debris seen on the tympanal side of the perforation edges had obviously entered the tympanum from the ear canal side during processing

The weak positivity of the mucus stains was localized mainly in the area of the higher epithelium of the hypotympanum AB positivity was clearly weaker than PAS-positivity The squamous epithelium was AB- and PAS-negative

4 2 TEMPORAL BONE 2

The patient had died at 56 of cerebral haemorrhage complicating acute myeloblastic leucaemia He had had discharge from his left ear periodically for 40 years. Otoscopy disclosed slight discharge and an extensive perforation of the pars tensa in the left ear

4.2 1 *Histology*

The central perforation comprised practically the whole pars tensa a good millimetre wide remnant (Fig 8) of the thickened (0 2—0 5 mm) drum membrane remaining throughout Its posterior part adhered to the medial wall of the tympanum (Fig 10) The squamous epithelium of the ear canal grew over the perforation edges for a short distance onto the tympanic side of the drum membrane (Fig 9) This ingrowth was most pronounced at the lower edge where the squamous epithelium extended up to 0 5 mm onto the tympanic side However it lost the surface keratin and stratum granulosum on the ear canal side just before the annular edge cuboidal columnar epithelium lining the abundant granulations of this area The Tympanic epithelial changes were difficult to evaluate since the *oedematous middle ear*

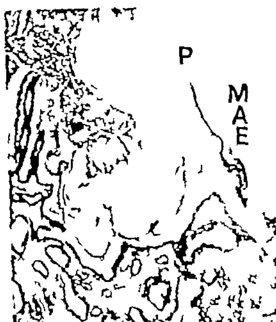


Fig 8 General view of the postero-inferior part of the tympanum showing the lower margin of the perforation Granular, thick mucosa covers the medial tympanic wall (MAE = meatus ac ext P = perforation edge) H—E



Fig 9 A closer view of the perforation edge in Fig 8 The squamous epithelium, devoid of its keratin cover and stratum granulosum, turns for a short distance over the edge onto the tympanal side H—E 160

Fig 10 1 1 mm posteriorly the level of Fig 8 The ear drum remnant adheres to the medial tympanic granulation (arrow) H—E



Fig 11 The point of adhesion in Fig 10 (arrow 11) The squamous epithelium both turns round the edge of the drum remnant (lower arrow) and continues to the surface of tympanal granulation tissue (upper arrow) Stratum granulosum and keratin are absent *H—E 160 x.*



union to the roof of the epitympanum The cariotic stapes was surrounded by fibrous tissue

The promontorial epithelium was cuboidal with 1—3 layers, and in some areas it even changed into flat endothelium-like lining In the posterior part of the middle ear the epithelium was highest at the floor where some of the epithelium had undergone a mucous change Hardly any secretory cells were seen in the tympanum. The tympanic mucosa was thick and oedematous Only in the medial wall was it somewhat fibrotic.

The anterior tympanum showed not only cuboidal and low columnar epithelium but also especially in the roof and in the lower parts, metaplastic type epithelium (the epithelium was multilayered the epithelial cells and nuclei were disorganized cytoplasm had shrunk and cellular eosinophilia had increased in H E staining) Backwards the metaplasia disappeared and was only seen in the neighbourhood of the perforation edges and over a small area in the upper medial wall of the posterior tympanum At the orifice of the Eustachian tube, the epithelium was largely of the respiratory type A strip of ciliated cells continued from the tube posteriorly in the lower and upper lateral parts of the middle ear to the posterior tympanum (Fig 7) Also a small strip of ciliated cells was seen on the luminal roof to the level of the posterior part of the promontory

Keratin stainings of the tympanic epithelium were negative The minute keratin debris seen on the tympanal side of the perforation edges had obviously entered the tympanum from the ear canal side during processing

The weak positivity of the mucus stains was localized mainly in the area of the higher epithelium of the hypotympanum AB-positivity was clearly weaker than PAS-positivity The squamous epithelium was AB and PAS negative

4.2 TEMPORAL BONE 2

The patient had died at 56 of cerebral haemorrhage complicating acute myeloblastic leucaemia He had had discharge from his left ear periodically for 40 years Otoscopy disclosed slight discharge and an extensive perforation of the pars tensa in the left ear

4.2 1 *Histology*

The central perforation comprised practically the whole pars tensa a good millimetre wide remnant (Fig 8) of the thickened (0.2—0 5 mm) drum membrane remaining throughout Its posterior part adhered to the medial wall of the tympanum (Fig 10) The squamous epithelium of the ear canal grew over the perforation edges for a short distance onto the tympanic side of the drum membrane (Fig 9) This ingrowth was most pronounced at the lower edge where the squamous epithelium extended up to 0 5 mm onto the tympanic side However it lost the surface keratin and stratum granulosum on the ear canal side just before the annular edge cuboidal columnar epithelium lining the abundant granulations of this area The Tympanic epithelial changes were difficult to evaluate since the oedematous middle ear

Fig 14 On the surface of the medial granulations in Fig 12 (Square 14) there is *apparently* nonmigrated squamous epithelium without stratum granulosum. H—E 160 x

Fig 15 Stratified squamous epithelium on the surface of granulation tissue in Fig 14 (square 15). Prickles are seen in the epithelial cells. The squamous epithelium shows scaling of pseudoparakeratotic character on its surface (arrow) H—E 400



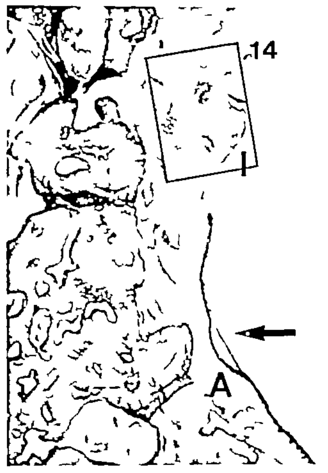


Fig 12 0.4 mm posteriorly to the level of Fig. 10. An inferior pseudomembranous adhesion (arrow) and, as its continuation squamous immigration (I) onto the surface of tympanal gra ulation are seen. (A = annular remnant.) H—E.

A

Fig 13 The inferior an lar remna t (A) and pseudomembranous adhesion seen i Fig 12 (the next section) The ep dermis w th ts strata continues to l the medial wall of the posterior tympanum H—E 40

Fig 14 On the surface of the medial granulations in Fig 12 (Square 14) there is apparently immigrated squamous epithelium without stratum granulosum. H—E 160 x.

Fig 15 Stratified squamous epithelium on the surface of granulation tissue in Fig 14 (square 15) Prickles were seen in the epithelial cells The squamous epithelium shows scaling of pseudoparakeratotic character on its surface (arrow) H—E 400





Fig 16 The lower margin of the perforation 2 3 mm anteriorly of the level of Fig 8 Medially of the ear drum remnant, extensive granulation can be seen (arrow) with squamous metaplasia on its surface (see Figs. 17 18) (MAE = meatus ac. ext T = tympanum TM = tympanic membrane remnant) H—E 20 x



Fig 17 In the lower lateral wall of the tympanum Fig 16 (square 17) squamous like epithelium of metaplastic type (M) is seen to change into columnar epithelium (arrow) with partial ciliary coating H—E 160

Fig 18 The junction of metaplastic squamous and columnar epithelium (arrow) in Fig 17 H—E 400



mucosa showed granulation tissue and areas of epithelial defects. It seemed, however that the squamous epithelium changed through a short (up to 0.5 mm) low metaplastic phase into cuboidal and columnar epithelium of the middle ear (Figs. 16—18).

In the anterior and superior margin of the perforation, the squamous immigration was almost absent. In the posterior margin, the squamous epithelium, having lost its granular and keratin layer immigrated along the ad hesions into the medial wall of the posterior tympanum (Figs. 10—13). There thus squa mous epithelium was widely stratified and contained even prickle cells. In some places, it showed pseudoparakeratosis, i.e. para keratotic scaling of superficial cells with their nuclei but without any sign of keratin in the squamous epithelium (Figs. 14 15) At a distance of about 2 mm from the drum edge the squamous epithelium changed into slightly metaplastic and, further on, into promontory was lined throughout with 1—3 layered cuboidal and in places columnar epithelium.

The middle ear epithelium was generally low cuboidal with 1—3 layers, and in some places even endothelium-like. The higher columnar epithelium, also seen in the tympa num was irregular throughout, and nume rous detached columnar cells were seen The columnar epithelium was localized particu larly in pouches and in hypotympanic air cells opening into the middle ear and in the anterior tympanum. Also, early stages of metaplastic epithelium were varyingly seen throughout the tympanum in the form of hyperplasia, increased disorganization, defor mity and increased eosinophilia of the cells.

No true glands or secreting cells were seen in the tympanum. There were a few cysts and pseudocysts mainly in the posterior parts. The auditory ossicles were carious. The thickened, remarkably oedematous mucosa of the middle ear was infiltrated by in flammatory cells.

The discontinuous epithelium of the an terior tympanum was largely columnar and, mainly in its roof and floor covered by cilia. No distinct strips of ciliated cells were visible. The cilia were most numerous in the lower parts of the tympanum and even there they ended posteriorly at the level of the anterior margin of the drum membrane. The Eustachian tube was covered by respiratory ciliated epithelium.

The areas of squamous and metaplastic epithelium in the middle ear failed to stain positively for keratin. The tympanic epi thelium stained weakly with PAS, and hardly at all with AB The cystic cavities were AB- and PAS-positive.

4.3 TEMPORAL BONE 3

This patient of 70 had died of carcinoma of the li er He had had chronic otitis media on the right for years. Otoscopy revealed a profusely draining central perforation of the pars tensa.

4.3.1 *Histology*

A central perforation, 3.5 mm wide and c. 3 mm high, downward from the umbo *level* was seen in the pars tensa (Fig. 19). The



Fig 16 The lower margin of the perforation 3 mm anteriorly of the level of Fig 8 Medially of the ear drum remnant, extensive granulation can be seen (arrow), with squamous metaplasia on it surface (see Figs. 17 18) (MAE = meatus ac. ext T = tympanum, TM = tympanic membrane remnant) H—E 20 x



Fig 17 In the lower lateral wall of the tympanum in Fig 16 (square 17), squamous like epithelium of metaplastic type (M) is seen to change into columnar epithelium (arrow), with partial ciliary coating. H—E 160 x

Fig 18 The junction of metaplastic squamous and columnar epithelium (arrow) in Fig 17 H—E 400 x



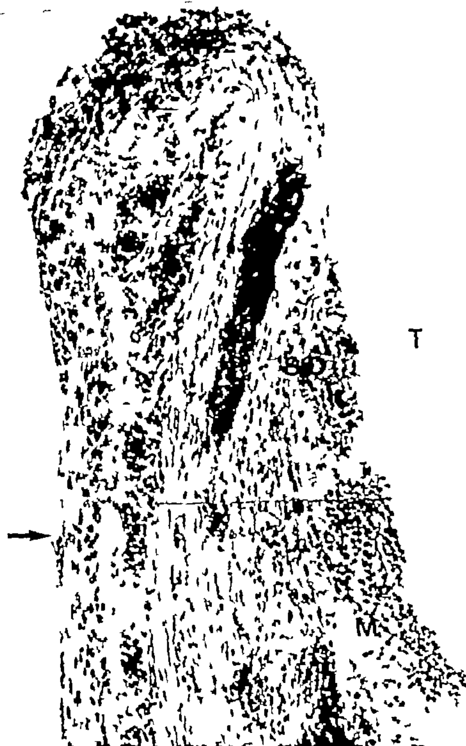


Fig. 2[illegible] A closer view of the lower perforation edge in Fig. 19. The squamous epithelium which [illegible] an attrition granuloma on the ear canal side (arrow) continues onto the tympanal side in [illegible] thinner form of 2—3 cell layers (SQ), and after [illegible] metaplastic phase of some 0.3 mm (M) it changes into columnar epithelium, which [illegible] 0.2 mm from the point of transition was ciliated. (T [illegible] tympanic) H—E 100

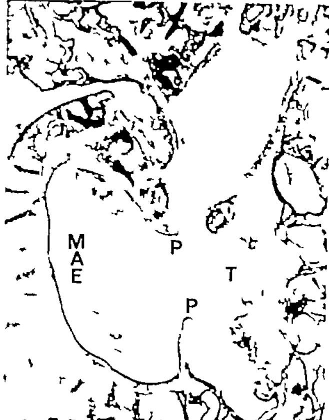
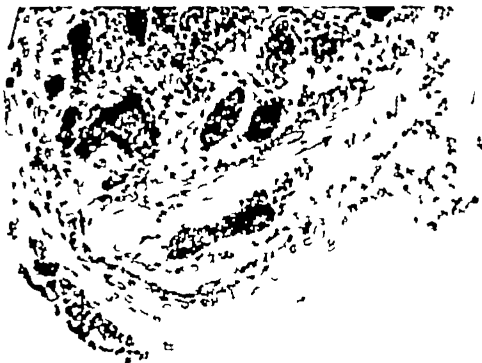


Fig 19 General view of the tympanum In the tympanal medial wall the section l vel runs posteriorly to the level of the wi dows. Perforatio of the pars tensa and the loose oedematous, thickened mucous membranes of the tympa um are isible Some puru lent udate is seen in the tympanum. (MAE = meatus ac. ext T = tympanum, P = perforation edge) H—E.



Fig 20 The upper margin of perforation and handle of the malleus, also seen in Fig 19 The squamou epithel um continues for a short d stanc onto the tympanic side (arrow) H—E 40 x.

Fig 1 A closer view of the perforation edge seen in Fig. 20. Stratum granulosum and keratin cover are abtent from the mmigrating squamous epithel m, and atypia caused by inflammation is seen i the epithelial cells. Vascularization in the drum stroma s abundant H—E 160 x.



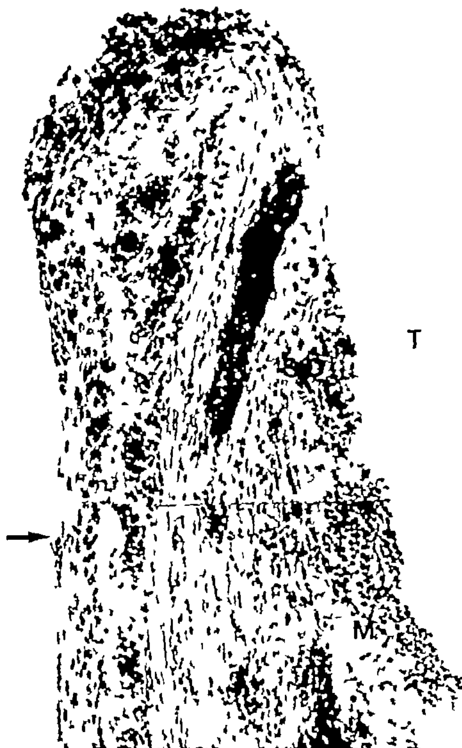
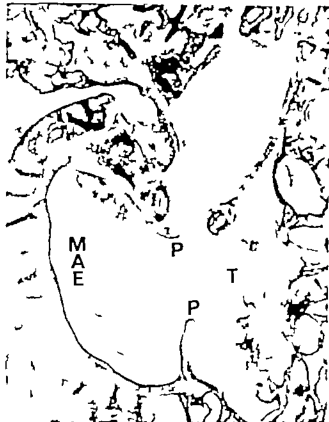


Fig. 22. A closer view of the lower perforation edge in Fig. 19. The squamous epithelium which loses its stratum granulosum on the ear canal side (arrow) continues onto the tympanal side in thinner form of 2—3 cell layers (SQ), and after a metaplastic phase of some 0.3 mm (M) it changes into columnar epithelium, which at 0.2 mm from the point of transition was ciliated. (T = tympanum.) H—E 120

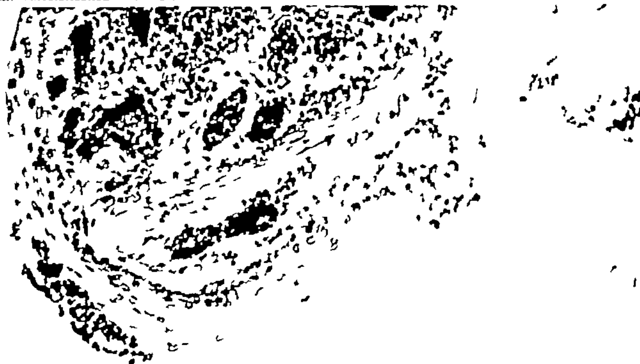


F g 19 General view of the tympa um In the tympanal medial wall the section level runs posteriorly to the l v l of the windows. Perforation of the pars tensa and the loose oedematous, thickened mucous membra es of the tympan m are visible Some purulent exudate is seen in the tympanum. (MAE = meatus ac c t., T = tympanum, P = perforation edge.) H—E.



F g 20 The upper margin of perforation and handle of the malleus, also seen Fig 19 The squamous epitheli m continues for a short distance onto the tympanic side (arrow) H—E 40 x.

F g 1 A closer view of the perforation edge seen in F g. 20. Stratum gra losum and keratin cover are absent from the immigrating squamous epithelium, a d atypia caused by nflammation is seen the epithelial cells. Vascularization the drum stroma is abu da t. H—E 160 x.



remaining drum was 0.2—0.3 mm thick. In the inferior margin of the perforation, the ear canal epidermis continued as squamous epithelium —3 layers thick (Fig. 22) onto the tympanic side of the drum for up to 1.0 mm, at its furthest extent reaching the lateral side of the inferior tympanum. All along the perforation edges, the epidermis lost its stratum granulosum on the ear canal side of th drum surface. No strata or keratini zation typical of epidermis, was seen on the surface of the squamous epithelium that had immigrated onto the tympanic side. In the upper edge of the perforation (Figs. 20, 21), the squamous epithelial immigration was similar in type and extent to that in the lower edge, while in the anterior and posterior edges it was of shorter extent. On the middle ear side after a short meta plastic phase, the squamous epithelium continued as cuboidal and respiratory epithelium, showing atypia due to active in flammation. On the ear canal side, perinuclear vacuolization was seen in the epidermis and inflammatory changes were also visible subepidermally

Pronounced inflammatory atypia was seen in the epithelium of the promontory and the whole middle ear cleft. In the area of the fossa ovalis, the epithelium had under gone a metaplastic change (independent metaplasia) into squamous epithel um a few (1—3) cell layers thick (Fig. 23). Similar epithelium was also seen on the mucosa of the roof of the middle ear space. However this could ha e been flat epithelium transformed by nflammatory atypia. Further more d stinct metaplastic areas without squamous arrangement were seen on the promontory surface (Fig. 24) and a small area on the floor of the anterior tympanum. There were extensive granulating surfaces (Fig. 25) and intensive organization processes which caused some difficulty in the determination of detailed localization and extent of the different forms of epithelium. However the respiratory type of epithelium seemed to be localized, in particular hypotympanally

In the anterior tympanum the respiratory epithelium had also retained its morphology more so in the lower parts. In the upper half of the anterior tympanum the epithelium showed prominent inflammatory atypia. In the upper lateral part flat epithelium of 1—2 layers was seen. In the roof the ciliated cells continued as two narrow strips which proceeded posteriorly to the umbo level. In feriorly the ciliary lining was more extensive and reached the level of the posterior part of the drum membrane. At the orifice of the Eustachian tube the epithelium was respira tory the cilia still being partly absent superiorly

The mucosa of the middle ear was consi derably thickened and, especially in the pouches, oedematous. Numerous organization processes of varying degree were seen. The subepithelium was infiltrated by inflamma tory cells. There were many pseudocysts. The auditory ossicles were cariotic and covered by thick mucosa.

Keratin stainings gave positive results neither for the tympanic metaplastic squa mous epithelium nor for the immigrating squamous epithelium from the drum membrane.

The tympanic epithelium stained weakly with PAS (the apical parts of some higher cells) and scarcely at all with AB Some PAS-positive granules were noted in the upper parts of the immigrating epidermis.



Fig 23 Metaplastic squamous epithelium (SQ) from the oval w ndow area Subepithelial pearls or pseudocysts (P) are visible The epithelial cells show in flammatory atypia (T = tympanal lumen) H—E 160 x

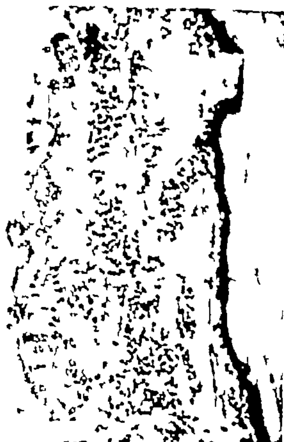


Fig 24 Epithel m of the anterior promontory show ng metaplasia a d nflammatory atypia. H—E 160 x



Fig 5 A org tio prox ak g pl h lat ral part of the a t rio t mpa m Th pithel m of respiratory type cha ges to endothel um l k hen it t rn to line you g g l sm sue I flammatory atyp i see in the p th lium H—I 100 x

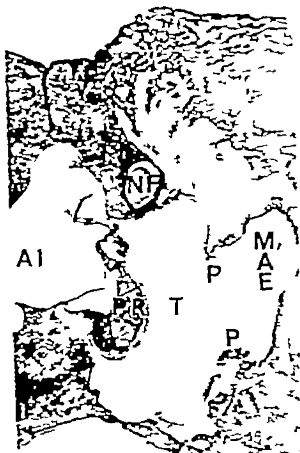


Fig. 26. General view of the tympanum. The section runs parallel to the level of the windows. (MAE = meatus ac. ext., T = tympanum, AI = aorta interna, NF = nervus facialis, PR = promontory, P = perforation edge.) H—E.

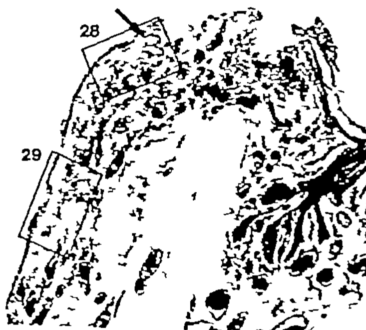


Fig. 27. A lower view of the lower margin of the perforation seen in Fig. 26. The tympanal edge of the perforation shows subepithelial accumulation of squamous epithelium (arrow), from which metaplasia-type epithelium continues onto the tympanal side. The granulating perforation ed... h... epithelial l... H—E.

4 4 TEMPORAL BONE 4

This patient had a history of pulmonary tuberculosis and had died at 59 in a chest hospital of a severe respiratory infection He had had impaired hearing in both ears. Otoscopy revealed an extensive central perforation of the pars tensa in the left ear drum Foul smelling discharge was found in the ear

4 4 1 *Histology*

Anteriorly and inferiorly the remnants of the drum membrane were less than 1 mm and *posteriorly 2 mm wide. Vertically the* perforation measured about 5 mm (Fig 26) The drum remnants, 0.5—1.0 mm thick were *increasingly fibrotic posteriorly* and ultimately slightly tympanosclerotic Granulation tissue was seen at the lower edge of the *perforation (Fig 27)*

The squamous epithelium of the ear canal immigrated around the lower part of the *perforation edge losing the stratum granu-*losum and its other epidermal characteristics just at the perforation edge It continued on *the tympanic side of the remaining drum* for some tenths of millimetres as squamous epithelium of 2—5 layers, and then changed into metaplastic (Fig 28) and in the lower medial angle of the drum into columnar partly ciliated epithelium (Fig 29) In the superior and posterior margin of the perforation the squamous epithelial immigration was very slight, and the squamous epithelium ended at the perforation edge (Fig 30) In the upper margin the squamous epithelium showed some tendency to growth in depth and sent projections of some 0.2 mm in length into the subepithelial connective tissue (Figs 31 32) In the junctional area the change was abrupt the epidermis changing into metaplastic and/or cuboidal epithelium losing its granular and keratin layer 0.1—0.2 mm before the junction (Figs. 31 32)

Squamous epithelial immigration was most *pronounced in the anterior margin of the* perforation where the epidermis grew up to 0.7—0.8 mm onto the tympanic side there *losing its keratinizing epidermal* character and was then transformed into metaplastic epithelium

The *epithelium of the promontory* was metaplastic (independent metaplasia) with eosinophilia in H E staining with disorganization *(Fig 35) and stratification (Fig 36)* of the epithelial cells. The cells showed a squamous structure in places, although the *epithelium had nowhere undergone the meta*plastic change into true squamous epithelium In the upper parts of the promontory this *epithelium was relatively thin 2—3 cell* layers, changing in the lower parts into considerably thicker epithelium In the hypo*tympanum its morphology began to suggest* a respiratory origin being partly lined by cilia

Slightly metaplastic epithelial lining was also widely seen elsewhere in the tympanal area Besides the promontory the tympanic floor and the medial surface of the perforation edges showed the most pronounced metaplastic changes *The mucosa of the upper* posterior part of the middle ear was lined by a low cuboidal epithelium of 1—2 layers (Fig 33)

The whole tympanal muscosa was thickened hyperplastic and especially meso- and hypotympanally hyperaemic The auditory ossicles were cariotic The lenticular process and a part of the long process of the incus were absent.

In the anterior tympanum the epithelium was still fairly widely metaplastic apparently respiratory in origin The change became slighter in degree towards the Eustachian tube (Fig 34) only increased eosinophilia and basal hyperplasia were seen (epithelium had 3—5 layers) From the tubal orifice onwards the epithelium assumed its

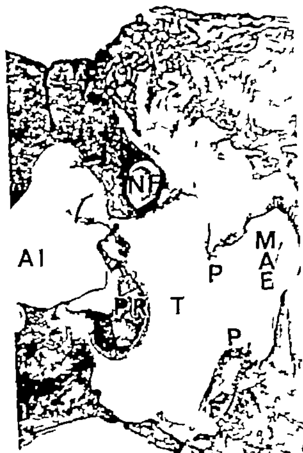


Fig. 26. General view of the tympanum. The section runs parallel to the level of the windows (MAE = meatus ac. ex., T = tympanum, AI = auris interna, NF = nervus facialis, PR = promontory, P = perforation edge.) H—E

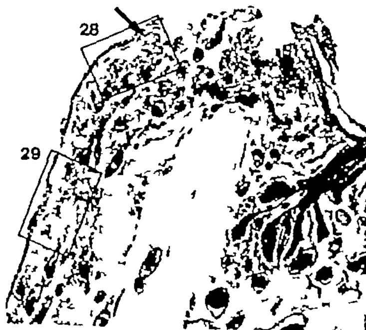


Fig. 27. A closer view of the lower margin of the perforation area in Fig. 26. The tympanal edge of the perforation shows subepithelial accumulation of squamous epithelium (arrow), from which metaplastic-type epithelium continues onto the tympanal side. The granulating perforation edge has no epithelial lining. H—E, 40

4 4 TEMPORAL BONE 4

This patient had a history of pulmonary tuberculosis and had died at 59 in a chest hospital of a severe respiratory infection He had had impaired hearing in both ears Otoscopy revealed an extensive central perforation of the pars tensa in the left ear drum Foul-smelling discharge was found in the ear

4 4 1 *Histology*

Anteriorly and inferiorly the remnants of the drum membrane were less than 1 mm and posteriorly 2 mm wide Vertically the perforation measured about 5 mm (Fig 26) The drum remnants, 0 5—1 0 mm thick were increasingly fibrotic posteriorly and ulti mately slightly tympanosclerotic. Granula tion tissue was seen at the lower edge of the perforation (Fig 27)

The squamous epithelium of the ear canal immigrated around the lower part of the perforation edge losing the stratum granulosum and its other epidermal characteristics just at the perforation edge. It continued on the tympanic side of the remaining drum for some tenths of millimetres as squamous epithelium of 2—5 layers, and then changed into metaplastic (Fig 28) and in the lower medial angle of the drum into columnar partly ciliated epithelium (Fig 29) In the superior and posterior margin of the perforation the squamous epithelial immigration was very slight, and the squamous epi thelium ended at the perforation edge (Fig 30) In the upper margin the squamous epi thelium showed some tendency to growth in depth and sent projections of some 0 2 mm in length into the subepithelial connec tive tissue (Figs 31 32) In the junctional area the change was abrupt the epidermis changing into metaplastic and/or cuboidal epithelium losing its granular and keratin layer 0 1—0 2 mm before the junction (Figs. 31 32)

Squamous epithelial immigration was most pronounced in the anterior margin of the perforation where the epidermis grew up to 0 7—0 8 mm onto the tympanic side there losing its keratinizing epidermal character and was then transformed into metaplastic epithelium

The epithelium of the promontory was metaplastic (independent metaplasia) with eosinophilia in H E staining with disorgani zation (Fig 35) and stratification (Fig 36) of the epithelial cells The cells showed a squamous structure in places although the epithelium had nowhere undergone the meta plastic change into true squamous epithelium In the upper parts of the promontory this epithelium was relatively thin 2—3 cell layers, changing in the lower parts into considerably thicker epithelium In the hypotympanum its morphology began to suggest a respiratory origin being partly lined by cilia

Slightly metaplastic epithelial lining was also widely seen elsewhere in the tympanal area Besides the promontory the tympanic floor and the medial surface of the perfora tion edges howed the most pronounced metaplastic changes. The mucosa of the upper posterior part of the middle ear was lined by a low cuboidal epithelium of 1—2 layers (Fig 33)

The whole tympanal muscosa was thicken ed hyperplastic and especially meso- and hypotympanally hyperaemic The auditory ossicles were carious The lenticular process and a part of the long process of the incus were absent.

In the anterior tympanum th epithelium was still fairly widely metaplastic appa rently respiratory in origin The change became slighter in degree t wards the Eu stachian tube (Fig 34) only increased eosi nophilia and basal hyperplasia were seen (epithelium had 3—5 layers) From the tubal orifice onwards the epithelium assumed its

Fig. 30. The upper perforation edge 0.2 mm anteriorly to the level of Fig. 26. A fibrotic, nearly 1 mm thick ear drum remnant is seen. At the tip of the perforation edge, the epidermis shows tendency to depth growth. H—E 40.



Fig. 31. The tip of the upper perforation edge in Fig. 30 (square 31). 0.2 mm before the junction, the epidermis loses the keratin cover and stratum granulosum (SG) whereas stratum spinosum continues right up to the junction. Subepithelial epidermal projections (without granular cells) growing towards the tympanum are also seen. H—E 160.

SG



Fig 8 The squamous epithelial accu- lation and ts continuation as metaplastic epithelium (M) in Fig 27 (square 28) can be seen Prickles appear in the accumula tion H—E 160 x



F g 29 A I g 7 (squa 29) Metaplastic epithel m (M) hanges t col mna ep thel um (R), with ment ci hary format ons (rrow) Th lia wer distinctly isibl 0 1 mm f rthe d H—E 160 x

Fig 30 The upper perforation edge 0.2 mm anteriorly to the level of Fig 26. A fibrotic, nearly 1 mm thick ear drum remnant seen. A: the tip of the perforation edge, the epidermis shows tendency to depth growth. H—E 40 x.



Fig 31 The tip of the upper perforation edge in Fig 30 (square 31). 0.2 mm before the junction, the epidermis loses the keratin cover and stratum granulosum (SG) whereas stratum spinosum continues right up to the junction. Subepithelial epidermal projections (without granular cells) growing towards the tympanum are also seen. H—E 160



Fig 28 The squamous epithelial accum lation and its continuation as metaplast epithelium (M) in Fig 27 (square 28) ca be seen. Prickles appear in the accumul tion. H—E 160 x.



F g 29 An area I g 27 (square 29) Metaplastic ep thel um (M) hanges into columnar epithel um (R) w th nc pient ci l ary formation (rrow) Th li were distinctly isibl 0 1 mm f rthe do H—E 160



Fig 30 The upper perforation edge 0.2 mm anteriorly to the level of Fig 26. A fibrotic, nearly 1 mm thick ear drum remnant is seen. At the tip of the perforation edge, the epidermis shows tendency to depth growth H—E 40

Fig 31 The tip of the upper perforation edge in Fig 30 (square 31). 0.2 mm before the junction, the epidermis loses the keratin cover and stratum granulosum (SG) whereas stratum spinosum continues right up to the junction. Subepithelial epidermal projections (without granular cells) growing towards the tympanum are also seen H—E 160

Fig 32 The area corresponding t Fig 31 0 2 mm anteriorly show simila changes H—E 160 x



F g 33 Upper medial p rt of the e drum remna t, correspond ng to the left marg f I g 30 (from the ne t section) co ered by low simple ubo dal pithel m The underlying stroma loose e cept the dense th con ect t sue layer de the basemen memb ne H—I 160



Fig. 34. Respiratory ciliated epithelium covering the medial tubotympanal wall. Numerous goblet cells are visible. Basal hyperplasia indicating incipient (= slight) metaplasia is seen. H—E 400 x.

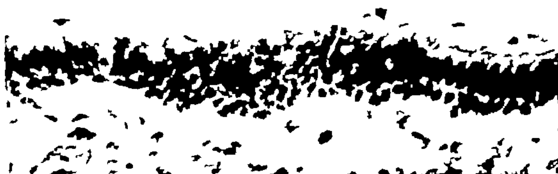


Fig. 35. Epithelial surface of the anterior promontory. Hyperplasia, disorganization and increased eosinophilia indicate metaplasia. E.g. the superficial epithelial layers [illegible] partially disorganized, and the ciliated columnar cells partially absent. Metaplasia is of [illegible] more pronounced degree than in Fig. 34. H—E 256 x.

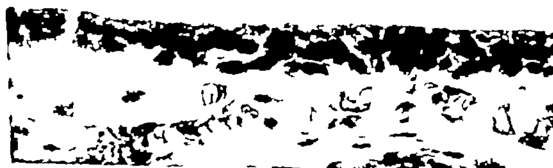


Fig. 36. Metaplastic epithelium of [illegible] the promontory surface 1.5 mm posteriorly to the Fig. 35 level. The epithelium is 2—3 layered, markedly eosinophil, and [illegible] number of the nuclei are tilted, suggesting [illegible] squamous arrangement. However no differentiation of cell layers is visible. The degree of metaplasia is more pronounced [illegible] E 400 x.

Fig 32 The area corresponding to Fig 31 0.2 mm anteriorly show similar changes. H—E 160 x.

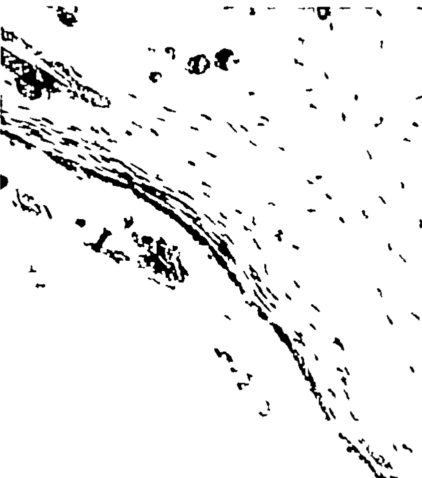


Fig 33 Upper middle part of the ear drum remnant corresponding to the left margin of Fig 30 (from the next section) is covered by low simple cuboidal epithelium. The underlying stroma is loose except the denser thin connective tissue layer under the basement membrane. H—E 160

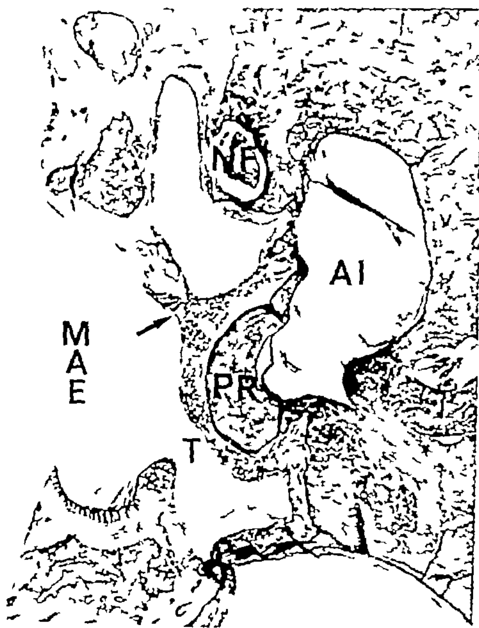


Fig. 37 General view. The whole tympanum, with thickened mucous membranes throughout, [illegible]. The upper edge of the ear drum perforation adheres (arrow) to the thickened, hy[illegible] mucosa of the promontory (MAE = meatus ac. ext., T = tympanum, AI = aditus [illegible], PR = promontory, NF = nervus facialis) H–E.

normal respiratory type Tubal epithelium showed a fair amount of mucus producing cells, including goblet cells. On the middle ear side, there were mucously changed cells only hypotympanally

The almost unbroken ciliary lining of the tube continued posteriorly into the middle ear in three strips a tapering ciliary strip of some 2 mm in the roof of the lumen another in the lower medial wall extending to the middle of the promontory and a third in the lower lateral area of the tympanum to the level of the posterior part of the drum membrane.

No keratin characteristics were disclosed in the metaplastic epithelium of the tympanum With AB and PAS the metaplastic epithelium stained fairly weakly with scattered positively staining cells. The respiratory epithelium stained moderately with both stains, while the squamous epithelium was AB- and PAS-negative

4.5 TEMPORAL BONE 5

The patient's medical history is given under Temporal Bone 4 Otoscopy disclosed an extensive, central perforation of the pars tensa in the right drum membrane. The ear canal contained foul smelling discharge.

4 5 1 *Histology*

The pars tensa showed a perforation (Fig 37) 4.2 mm wide and c. 4 mm high Anteriorly and inferiorly about 1 mm of drum membrane remained and posteriorly the remnant was 2.5 mm wide. The membrane was fibrotic, 0 5—1 0 mm thick. Especially the inferior and posterior margin of the perforation was granulating infiltrated by inflammatory cells, and partly necrotic (Fig 42)

In the inferior margin the ingrowing epidermis lost its characteristics on the ear canal side of the drum and proceeded over the edge onto the tympanic side for a distance of 0 5—1 0 mm as squamous epithelium of 1—3 layers (Fig 40) Through a metaplastic zone of 0.2—0 3 mm a further change into columnar and soon into ciliated epithelium occurred (Fig 41) Although the epithelium was partly absent from the sligtly granulating surface of the lower perforation edge, the squamous epithelium could be seen to continue beyond the edge

The edge of the postero-superior quadrant of the perforation from the umbo backwards, adhered to the mucosa of the promontory (Fig 38) Along this adhesion the squamous epithelium of the ear canal immigrated to the tympanic side losing its rete pegs at the edge of the perforation It proceeded as 2—3 cell layered squamous epithelium along the partly ulcerated surface of the promontory (Fig 39) for 1.5—2 0 mm towards the anterior and inferior part of the promontory and then transformed through a metaplastic zone of 0.2—0.3 mm into columnar epithelium. Anteriorly of the adhesion in the upper free margin of the perforation the squamous epithelium changed abruptly into tympanic cuboidal epithelium

In the posterior margin of the perforation corresponding to the promontorial adhesion the squamous epithelium consisted of several layers. It had a stratum spinosum, and basally it sent projections into the underlying connective tissue e g at the oval window area, where it even formed a small subepithelial

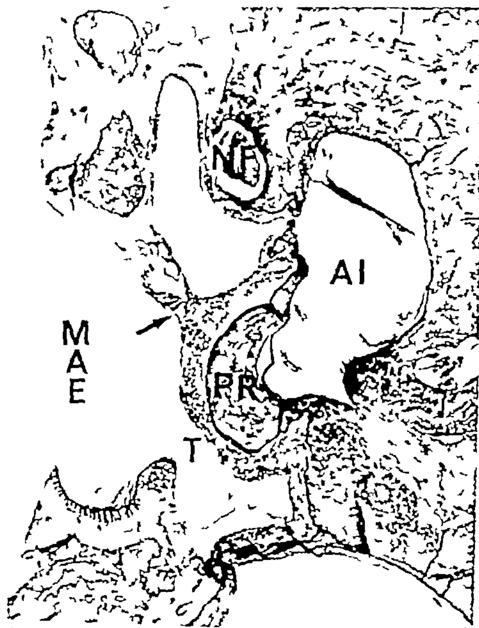


Fig. 37 General view. The whole tympanum, with thickened mucous membranes throughout, visible. The upper edge of the ear drum perforation adheres (arrow) to the thickened, hyperaemic mucosa of the promontory (MAE = meatus ac. ext., T = tympanum, AI = auris interna, PR = promontory, NF = nervus facialis) H–E.

normal respiratory type Tubal epithelium showed a fair amount of mucus producing cells including goblet cells. On the middle ear side, there were mucously changed cells only hypotympanally

The almost unbroken ciliary lining of the tube continued posteriorly into the middle ear in three strips a tapering ciliary strip of some 2 mm in the roof of the lumen another in the lower medial wall extending to the middle of the promontory and a third in the lower lateral area of the tympanu to the level of the posterior part of the dru membrane.

No keratin characteristics were disclos in the metaplastic epithelium of the tymp num. With AB and PAS the metaplast epithelium stained fairly weakly wit scattered positively staining cells. The resp ratory epithelium stained moderately wit both stains, while the squamous epitheliu was AB and PAS-negative

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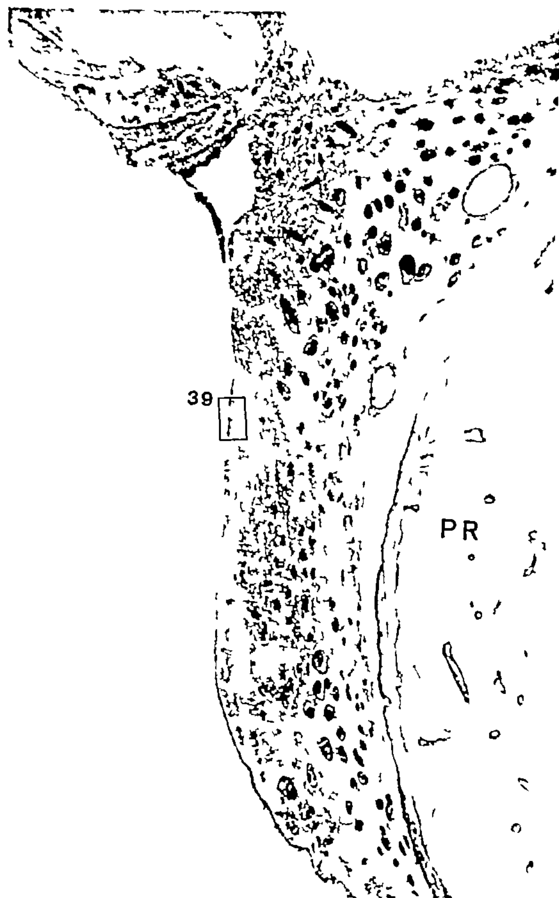
In the inferior margin the ingrowing epidermis lost its characteristics on the ear canal side of the drum and proceeded over the edge onto the tympanic side for a distance of 0 5—1 0 mm as squamous epithelium of 1—3 layers (Fig 40) Through a metaplastic zone of 0.2—0.3 mm a further change into columnar and soon into ciliated epithelium occurred (Fig 41) Although the epithelium was partly absent from the sligtly granulating surface of the lower perforation edge the squamou epithelium could be seen to continue beyon the edge

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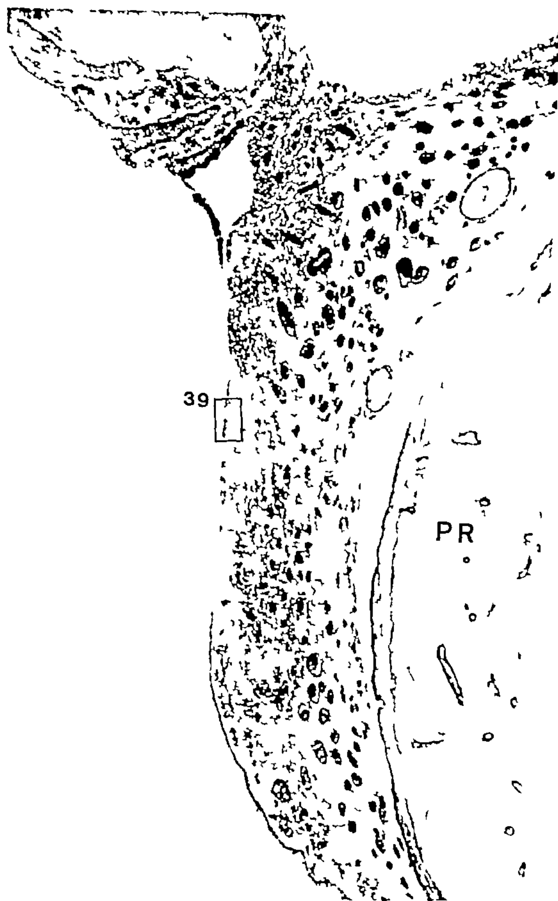
Fig. 39. Promontorial immigrating squamous epithelium in Fig. 38 (square 39). The epithelium consists of 2–3 layers of cells, and has no epidermal characteristics. H–E 4[illegible]



F g 3* A closer he adhesion nd promontorial mucosa seen also F g 37 Along the b dg of dhes h sq mou epithel um of the ar drum conti ues onto the r f f the hyperaem p omontorial mucosa. At th point f dhesion, the squamous m send p to the subep thelial tissue (PR = promontory) H—E 4



Fig. 39 Promontorial area growing squamous epithelium in Fig. 38 (square 39). The epithelium consists of 2—3 layers of flat cells and has no epidermal characteristics. H—E 420 x.



F g 39 A loser ʌ f h dhesion and promon orial mucosa seen lso in Fig 37 Along the bridge of adhes n the squamous epithelium of the ear drum continues onto the sur fa of the hyperaem promon ri l mucosa At the point of dhesion, the squamous epi- h m sends pr jons n he subepithelial tissue (PR = promontory) H—E 40 x.



Fig. 39. Promontorial [illegible] squamous epithelium in Fig. 38 (square 39). The epithelium consists of 2–3 layers of [illegible], and has no epidermal [illegible]. H–E [illegible]

Fig 40 A closer view of the lower margin of the perforation edge in Fig. 37 On the ear canal side, the epidermis loses its stratum granulosum (arrow) and continues over the granulating perforation edge as an ever thinner squamous epithelium (SQ) and, on the tympanal side through a metaplastic phase (M) changes into higher columnar epithelium (R) H—E 40 x



Fig 41 Tympanal side of the lower perforation edge seen in Fig. 40 (square 41) Immigrating squamous epithelium (SQ) through metaplastic phase (M) changes to columnar epithelium (R) with even cilia on its surface (arrow) H—E 160 x



Fig. 42. General view of the tympanum 1.3 mm posteriorly to the Fig. 37 level. The perforation edges are linked together by promontorial adhesion. The tissue of the middle inferior bridge is necrotic in the middle (arrow). The auditory ossicles are cariotic and the long process of the incus is broken by necrosis. The square shows keratin cyst (see Fig. 43). H–E.



Fig. 43. The area below the incudostapedial joint in Fig. 42 (square 43). The epidermis sends into the underlying connective tissue squamous epithelial projection, which forms small keratin... H–E ×1

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Fig 41 Tympanal side of the lower perforation edge seen in Fig 40 (square 41) Immigrating squamous epithelium (SQ) through a metaplastic phase (M), changes to columnar epithelium (R) with even cilia on its surface (arrow) H—E 160 x.

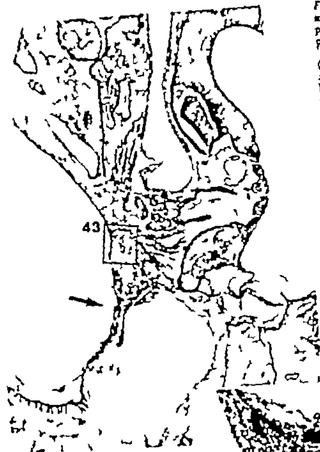


Fig. 42. General view of the tympanum 1.3 mm posteriorly to the Fig. 37 level. The perforation edges are linked together by promontorial adhesion. The tissue of the middle anterior bridges is necrotic. In the middle (arrow). The auditory ossicles are carious and the long process of the incus is broken by necrosis. The square shows a keratin cyst (see Fig. 43). H–E.



Fig. 43. The area below the [illegible] pedicle [illegible] in Fig. 42 (square 43). The epidermis and [illegible] the underlying connective tissue [illegible] epithelial process, which forms small keratin cysts. H–E [illegible]

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Fig 41 Tympa l sid of the lower perforation edge seen in Fig 40 (square 41) Immigrating squamous epithelium (SQ), through a metaplasti phase (M), changes into colum ar epithel m (R) with en cilia on its surfac (arrow) H—E 160 x.

keratin cyst (Figs. 42, 43). This squamous epithelium was not that of the promontory but that of the adhesive edge of the drum membrane. Also elsewhere along the edges of the perforation the squamous epithelium showed some tendency towards growing into depth sending projections some tenths of millimetres long into the underlying connective tissue.

In the postero-inferior margin of the perforation a squamous epithelial immigration, similar to that of the lower margin, extended about 0.5—0.6 mm onto the tympanic side of the drum membrane. In the anterior margin, the thicker squamous epithelium which had retained its stratum spinosum, grew up to 0.4—0.5 mm onto the tympanic side (Fig. 45), changing into tympanic cuboidal epithelium through a short transitional area.

The middle ear epithelium was mainly of the columnar type occasionally even 2—3 cell layers thick. In the upper part of the tympanum, there was also low cuboidal and sometimes even flat epithelium. The mucosa was thick, hyperplastic and hyperaemic. A few glands (Fig. 44) and cysts were seen and there was abundant lymphocyte infiltration of the subepithelial tissue. The auditory ossicles were cariotic. Only a remnant of the lenticular process of the incus was seen, and the connection to the head of the stapes was fibrotic.

Cilia were seen in the anterior tympanum, mainly in its lower parts, from where a hypotympanal strip of ciliated cells extended to the posterior parts of the middle ear. The medial wall showed a smaller ciliated cell track which extended to the anterior parts of the promontory.

The Eustachian tube had a complete ciliary lining with a pseudostratified columnar epithelium of the respiratory type. A few goblet cells were seen.

No keratinization, apart from the keratin cyst (see above), was detected on the tympanic immigrated squamous epithelium. Mucus stain of this epithelium did not show any positivity. The respiratory epithelium, particularly the apical parts of the cells, stained generously both with AB and PAS, however not as an unbroken carpet but interspersed with unstained cells.

4.6 TEMPORAL BONE 6

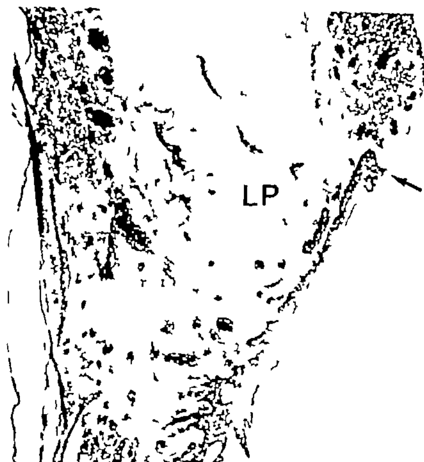
The patient had died at the age of 11 of pneumococcal meningitis which had developed as a complication to chronic otitis media on the left. Otoscopy disclosed a central perforation in the drum membrane involving approximately half the pars tensa. The tympanum was moist, no true purulent discharge was seen.

4.6.1 *Histology*

The pars tensa had a central perforation measuring 3 mm vertically and 2.5 mm horizontally. At its narrowest, the remaining drum membrane margin measured over 1.5 mm. The fibrotic remnants were thickened, up to 0.5 mm. The squamous epithelium of



Fig 44 A gland from the inferomedial wall of the posterior tympanum. H—E 51 x



F g 45 Ea drum rem ant n front of the p foration The f b-rous *lam propria (LP)* s al dy partly bsent The squamous ep th l um has mm grated from the ear can l nd *(left)* o e the perforation edge onto the tympanal nd wher the stra tum gran losum s abse t or detached Prickles were seen up to the junction (rrow) The epithe l um sends projections into the underlying connect tss of the ea drum H—E 40 x.



[illegible] 49. 2 mm posteriorly to the Fig. 46 level. This section shows how the squamous epithelium, just anterior to the perforation, intrudes into the subepithelial [illegible] drum stroma of the tympanal side. (T [illegible] tympanum.) H—E 165.



Fig. 50. The extreme anterior edge of the perforation showing the merely epithelial continuity of the drum membrane. No immigration. (T = tympanum.) H—E 45.

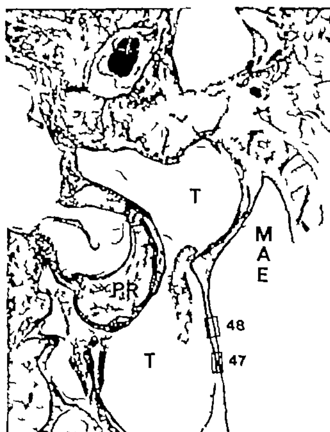


Fig 46 General view of the tympanum 0.4—0.5 mm anteriorly to the perforation. (MAE = meatus a. ext., T = tympanum PR = promontory) H—E

Fig 47 (bottom left) A part of the ear drum in Fig 46 (square 47) The squamous epithelium of the ear canal side has grown without stratum granulosum, under the tympanal epithelium, with a thin fibrotic connective tissue layer of 0.02—0.03 mm remaining between the epithelial layers. (T = tympanum) H—E 160 x

Fig 48 (bottom right) An area seen in Fig. 46 (square 48) A distinct subepithelial streak of squamous epithelium is still visible on the tympanal side (T) The ear drum is fibrotically thickened (in the figure up to 0.2 mm) The connective tissue layer between the squamous streak and the partly ciliated tympanal epithelium is rich in fibrocytes. H—E 160 x.





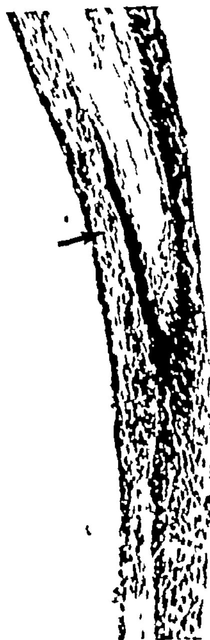


Fig. 49. 0.2 mm posteriorly to the Fig. 46 level. This section shows how the squamous epithelium, just anteriorly to the perforation, intrudes into the sub-epithelial ear drum stroma of the tympanal side (arrow). (T = tympanum.) H—E 160.



Fig. 50. The extreme anterior edge of the perforation showing the merely epithelial continuity of the drum membrane. No immigration. (T = tympanum.) H—E 40.

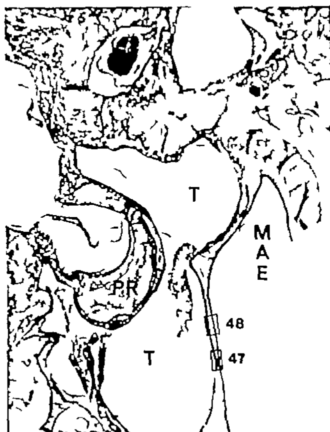


Fig 46 General v ew of the tympanum 0.4—0 5 mm anteriorly to the perforation (MAE = meatus ac. ext., T = tympanum PR = promontory) H—E.

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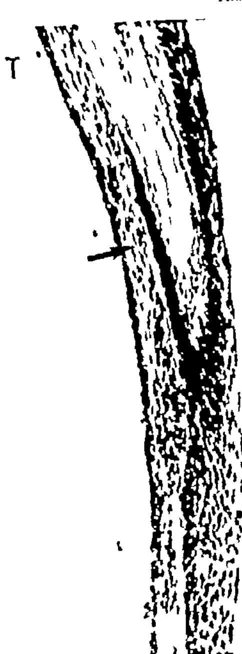


Fig. 49. 0.2 mm posteriorly to the Fig. 46 level. This section shows how the squamous epithelium, part anteriorly to the perforation, intrudes into the sub-epithelial ear drum stroma of the tympanal side (arrow). (T = tympanum.) H—E 160



Fig. 50. The extreme anterior edge of the perforation showing the merely epithelial continuity of the drum membrane. No immigration. (T = tympanum.) H—E 40

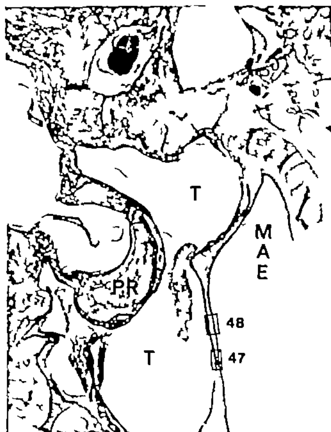


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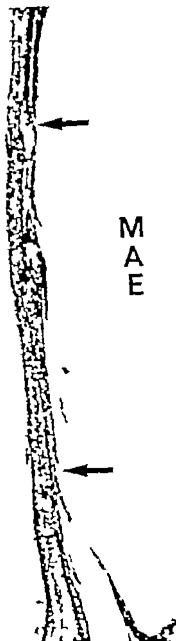


Fig. 34. 0.3 mm posteriorly to the perforation. Because of eversion of tympanal epithelium, the squamous epithelium is extensively absent (area between arrows) from the ear canal side of the drum. (MAE = meatus ac. ext.) H—E 43

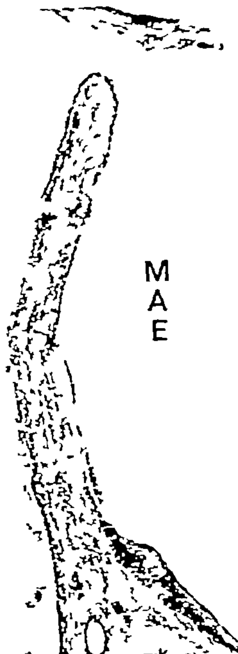


Fig. 35. The lower perforation edge some 0.1 mm posteriorly to the vertical level of the anterior perforation edge. On the ear canal side (MAE) of the drum, squamous epithelium is absent over a distance of 0.9 mm. The lining epithelium is 1—3 layered, cuboidal eversion epithelium. H—E 4 x.

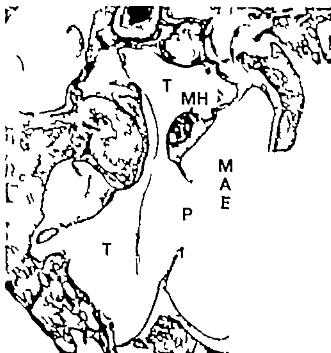


Fig 51 General view of the tympanum 1.0 mm posteriorly to the Fig 46 level. (MAE = meatus ac xt. T = tympanum MH = malleus handle P = perforation.) H—E.



Fig 52 (bottom left) A closer view of the upper perforation edge (the next section to Fig. 51 level): the ear canal epidermis changes abruptly into cuboidal tympanal epithelium (arrow) H—E 100 x.



Fig 53 (bottom right) A closer view of the lower perforation edge in Fig 51 showing the abrupt junction (arrow). H—E 100 x.

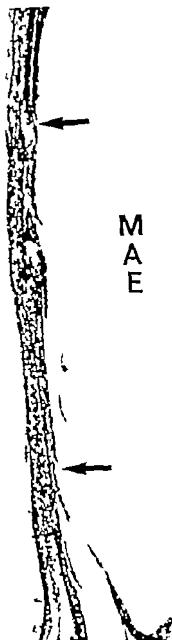


Fig. 34. 0.3 mm posteriorly to the perforation. Because of eversion of tympanal epithelium, the squamous epithelium is extensively absent (area between arrows) from the ear canal side of the drum (MAE = meatus ac. ext.) H—E 40

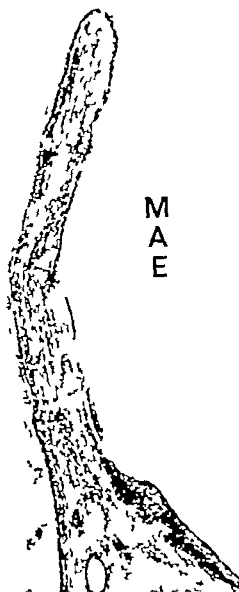


Fig. 35. The lower perforation edge some 2.1 mm posteriorly to the vertical level of the anterior perforation edge. On the ear canal side (MAE) of the drum, squamous epithelium is absent over distance of 0.9 mm. The lining epithelium is 1—3 layered, cuboidal eversion epithelium. H—E 40 x.



F g 56 The upper perf ration edge at Fig 55 le 1 Eversion (0 1 mm) onto the ea canal side (MAE) is seen. The ear drum stroma is relatively fibrotic, yet abundantly vascularized H—E 160 x.

the ear canal did not immigrate onto the tympanal surface but transformed abruptly at the edge of the perforation into ordinary tympanic epithelium (Figs. 50—53) On the other hand, the squamous epithelium project ed, just before the anterior edge of the perforation, into the ear drum stroma. It grew underneath the partly ciliated tympanic epithelium leaving a connective tissue strip 0.01—0.03 mm thick between the epithelia (Figs. 46—49) This ingrowth continued a good 1 mm forward, about 1 mm upward and about 0.2 mm downward from the anterior edge of the perforation. Elsewhere in the perforation edges no epithelial ingrowth was noted.

At the perforation edges, antero-posteriorly the cuboidal epithelium of 1—2 layers evert ed increasingly onto the ear canal surface of the drum remnants (Figs. 54—56). Even here, however the epidermal junction was abrupt. Posteriorly the eversion was most pronounced (up to 1.0 mm) in the inferior edge of the perforation (Fig 55) weakening upwards until, in the postero-superior edge (Fig. 56) it was 0 15 mm. In the area of the pronounced eversion, the otherwise fibrotic stroma of the drum membrane showed moderate vascularization (Fig. 56), suggesting myringitic etiology of the eversion.

The type of epithelium on the promontory and the whole tympanum, was variable. The promontorial epithelium was mainly cuboidal, metaplastic and mucously changed. The degree of metaplasia was relatively low its principal signs were the disorganization and hyperplasia of the epithelial cells, and the increased eosinophilia of cells in some places. Mucously changed epithelium on the promontory was confined mainly to its lower half

In addition to these epithelial types, some columnar epithelium was also seen tympa nally Usually the higher (columnar mucous) epithelium was confined to the anterior and inferior parts of the middle ear and the lower cuboidal to the superior parts and antrum. The localization of the different epithelial types, however varied greatly Besides the medial wall, epithelial metaplasia was also varyingly seen at the floor of the tympanum, and also in the epitympanal space. The width of the zones of metaplasia varied from 0.1 to 1.0 mm. Nowhere in the tympanic area was there any sign of even elementary squamous epithelium.

The Eustachian tube was lined by respi ratory epithelium, excepting the roof of its orifice, where the epithelium was still mucously changed. The respiratory epithelium of the tympanal tube showed extensive hy perplastic areas, up to a thickness of 5 cell layers. Posteriorly the ciliation continued in fero-laterally lining also a part of the lower medial surface of the ear drum and extending as a tapering and weakening strip to the posterior part of the middle ear

The ossicular chain was intact. The tympa nic connective tissue layer was slightly thickened, relatively fibrotic and showed some lymphocytic infiltration. Hardly any glands were seen. Pseudocysts were numerous, and there were adhesions indicating an organization process.

Keratin stainings showed no positive reac tions on the tympanic side. The tympanic epithelium was positive to both of the two methods of mucus staining, but the response to PAS appeared slightly more pronounced.



Fig 56 The pper perforation edge t F g 55 lev l Eversion (0 1 mm) onto the ea canal side (MAE) is seen The ear drum stroma is relati ly fibrotic, yet abunda tly vascularized H—E 160

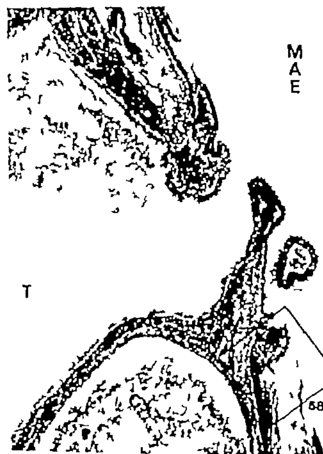


Fig 57 Perforation the centre of pars tensa. Chronic myringitis is seen in the perforation edges, associated with eversion of tympanic epithelium. A extensive cystic cavity (Cy) is visible. (MAE = meatus ac ext T = tympanum) H—E 40



Fig 58 The lower perforation edge from the ea canal side, also seen in Fig 57 (square 58) The epidermis with all its layers extends to the abrupt junction where thickens and pushes the eversion epithelium partly off its base H—E 160

4.7 TEMPORAL BONE 7

This patient, at the age of 70 had died of hepatic coma. In the hospital it had been noticed that her left ear was draining Otoscopy disclosed a central perforation of the pars tensa. Above the perforation the ear drum adhered to the promontory and the medial wall of the tympanum Profuse purulent exudate was seen in the ear

4 7 1 *Histology*

There was a 1.5 mm high and 3 mm wide perforation of the pars tensa. The perforation edges were covered by heavily fibrotized, partly polypotic granulation tissue The tympanic epithelium containing numerous goblet and other secretory cells, but otherwise with a relatively well *retained respiratory* structure everted all over the perforation edges onto the ear canal side of the ear drum for a distance of up to 1 mm (Fig 57) At the junction the tympanic epithelium changed into epidermis either abruptly (in the lower edge, Fig 58) or through a zone of squamous *metaplasia of a maximal width of 0.5 mm* (in the upper edge, Fig 57) At many points in the junction the epidermal and the ciliated columnar cells were seen side by side All along the junction there were also places where the epidermis grew under the columnar epithelium for distances of 0 1—0 2 mm detaching the columnar epithelium from its basement membrane (Figs. 59 60) The epidermis nowhere extended to the edge of the perforation but was displaced by tympanic eversion epithelium which had developed on a *myringitic basis (Figs 57 59)*

The basal cell layer of the eversion epithelium appeared thickened throughout (Figs. 59 61) forming a stratum of cells of a squamous appearance, of 2—3 or even 5 layers This perhaps *represented* partly basal hyperplasia and partly an artifact produced by the sectioning

Above the perforation the fibrotically thickened (up to 0.5 mm) ear drum adhered to the mucosa of the upper promontorial and the oval window area, forming at the horizontal level of the facial canal a bridge of adhesion from the upper edge of the ear canal thus partly obliterating the epitympanum The epithelial lining of the promontory and of the tympanum on the whole, was high columnar and markedly mucous. Goblet cells were very numerous, and there were *also secretory columnar cells* and, in some places in the superficial parts of the epithelium atypical secretory cells. The tympanum showed also areas where the columnar epithelium was almost entirely replaced by the basophilic mucus epithelium. Only in the epitympanum was the epithelium *lower cuboidal and of 1—2 layers.*

In the anterior tympanum, apart from the roof the epithelium was ciliated Posteriorly with marked mucosity predominating the epithelial picture the ciliation diminished and localized itself mainly on the floor epithelium. It extended farthest as a tract *covering the medial surface* of the inferior ear drum remnants, gradually tapering into an infero-lateral strip and ending in the sinus tympani A fairly well preserved ciliary lining was also seen on the polypotic granulation tissue of the perforation edges, both on the tympanic and the ear canal side. In the Eustachian tube the epithelium was ciliated respiratory but even there the mucosity was pronounced. At the roof of the tubal orifice, the epithelium had no cilia.

Of the auditory ossicles, only a cariotic *stapes was visible* The middle ear mucosa was considerably thickened and fibrotic In the pouches the stroma was looser and oedematous. An infiltration of inflammatory cells was seen subepithelially Numerous *cysts were seen* The exudate of the middle ear lumen contained granulocytes

Keratin stainings gave no positive reactions on the tympanic side On the ear canal

Fig. 60 The upper squamo-columnar junction in Fig. 59 (square 60). The epidermis abruptly changes into mucous epithelium and partly slides under it (S). The epidermis also sends a projection (arrow) into the subepithelial tissue. H—E 235 x.



Fig. 61 The area of eversion epithelium seen in Fig. 59 (square 61). The epithelium is highly mucous, and pronounced basal hyperplasia is seen in its deeper layers. H—E 400

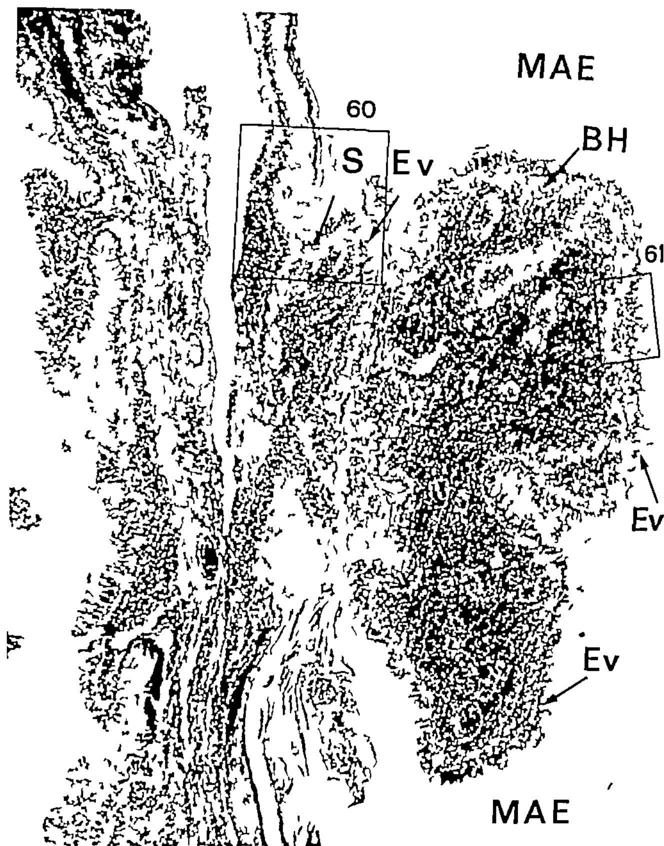


Fig 59 Ear drum 0 5 mm terio ly to the perforati dg A polypot f rmation is ubl on the ear canal sd (MAE) The tympanal p thel um rsion (L) on the ar ca l side The type f the ev rsion ep thelium resp ratory and mucous, d t ha reta ed ts l to fa rly great e tent The figure lso bows a l d g squamo-c l mna junct on (S), and extensi basal *hyperplasia (BH)* the ver sion epithel m H—E 40



Fig 60 The upper squamo-columnar junction in Fig 59 (square 60). The epidermis abruptly changes into mucous epithelium and partly slides under it (S). The epidermis also sends a projection (arrow) into the subepithelial tissue. H—E 235 x.

Fig 61 The area of eversion epithelium seen in Fig 59 (square 61). The epithelium is highly mucous, and pronounced basal hyperplasia is seen in its deeper layers. H—E 400

side of the drum, the epidermis kept its stratum granulosum and the keratin cover up to the junction where keratin formation was partly parakeratotic in character

Mucus stainings gave a strong response in the tubal and tympanic epithelium showing AB and PAS- positivity also in the ciliated cells The metaplastic transitional areas stained considerably better with PAS The superficial parts of the epidermis close to the perforation stained faintly with PAS alone.

4 8 TEMPORAL BONE 8

This 51 year old patient had died of coronary thrombosis in a chest hospital where he had been treated for pulmonary tuberculosis He had had bilateral chronic ear disease since childhood Otoscopically the left ear showed a large nearly total defect of the pars tensa A small remnant of the fibrous annulus could be seen in all areas. There was purulent exudate in the ear canal

4 8 1 *Histology*

At the floor of the ear canal the canal epidermis grew over the fibrous annulus to the hypotympanal area retaining its epidermal characteristics for a distance of 0.3—1 0 mm (Figs 65—68) Thereafter it changed into metaplastic type epithelium of 3—5 layers which lined the main part of the hypotympanum Before reaching the promontory surface it changed into a mucous type of epithelium containing numerous goblet cells and some ciliated cells, to transform again on the promontory into metaplastic epithelium At the tympanal side of the fibrous annulus, the continuation of ear canal epidermis showed distinct subepithelial growth for a length of about 1 mm into the hypotympanal stroma (Figs 65 67 68)

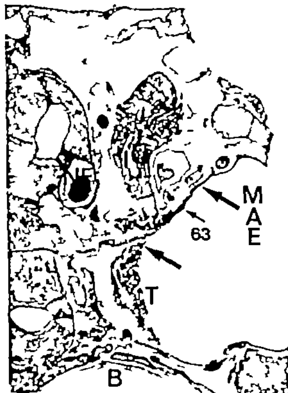
In the upper edge of the perforation the remnants of the drum adhered to the malleus handle and to the long process of the incus through which a bridge of adhesions connected it to the promontory surface (Fig 62). Along this bridge the keratinizing squamous epithelium from the ear canal was seen to continue to the level of umbo and close to the long process of the partly necrotic incus. From this point it continued as a nonkeratinizing metaplastic type squamous epithelium (junction metaplasia) towards the promontory (Figs 62—64) On the promontory it proceeded as a metaplastic epithelium and changed in the posterior part of the promontory into mucus producing columnar epithelium The latter epithelium also covered the posterior hypotympanum and here the nonkeratinizing squamous epithelium (junction metaplasia) was limited to the proximity of the perforation edge (less than 1 mm distance) Taking the perforation as a whole, the keratinizing squamous epithelium immigrated for a short distance towards the tympanum then lost its granular cell layer and overlying keratin and continued as a thinner metaplastic type of non keratinizing squamous epithelium (for a distance of 0 1—1 0 mm) before changing into other epithelial types.

The tympanal mucous membrane was thick loose and oedematous Ciliated epithelium was mainly seen as two strips, one running medially on the anterior promontory

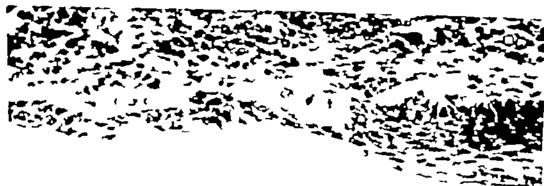
Fig 62 General view of the tympanum posteriorly to the level of the windows. Carious incus and superior adhesion (arrows) to the tympanal wall are seen. The loose stroma shows follicular lymphocyte accumulations, and the tympanic cavity contains exudate. (NF = nervus facialis, MAE = meatus ac. ext. I = incus, B = bulbus jugularis, T = tympanum.) H—E.

Fig 63 (middle). The epidermal junction in the bridge of adhesion in Fig. 62 (arrow 63), laterally to the long process of the incus. 0.1 mm before the junctional area the epidermis loses its stratum granulosum and its keratin cover and then changes into thinner metaplastic squamous epithelium. The epidermis, before the junction, also sends two short subepithelial projections. H—E 64

Fig 64 (bottom). The change of the squamous epithelium into squamous metaplasia, seen in Fig. 63 (square 64). The prickles were seen almost up to the line of change. H—E 160







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4 8 TEMPORAL BONE 8

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Fig. 62 General view of the tympanum posteriorly to the level of the windows. Cariotic incus and superior adhesion (arrows) to the tympanal wall are seen. The loose stroma shows follicular lymphocyte accumulations, and the tympanic cavity contains exudate. (NF = nervus facialis, MAE = meatus ac. ext., I = incus, B = bulbus jugularis, T = tympanum) H—E.

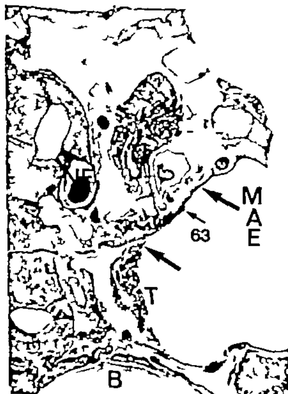


Fig. 63 (middle) The epidermal junction in the bridge of adhesion in Fig. 62 (arrow 63), laterally to the long process of the incus. 0.1 mm before the junctional area the epidermis loses its stratum granulosum and its keratin cover and then changes into thinner metaplastic squamous epithelium. The epidermis, before the junction, also sends two short subepithelial projections. H—E 64 x.

64

Fig. 64 (bottom) The change of the squamous epithelium into squamous metaplasia, seen in Fig. 63 (square 64). The prickles were seen almost up to the line of change. H—E 160



Fig 65 The lower margin of the perforation, 0.2 mm anteriorly to the level of Figs. 62—64 Superficial and subepithelial ingrowth of epidermis is seen. The keratin characteristics continue al most to the junction (upper arrow) The hypotympanal stroma is loose and oedem tous. Subepithelial follicular lymphocyte infiltration can be seen (lower arrow). (A = annulus membr tymp T = tympa um, MAE = meatus ac. ext.) H—E 40 x



F g 66 The epithelial transitional rea seen also in Fig 65 (from the upper arrow down ds) The epidermi (E), fter a short (p to 1 0 mm) squamous metaplastic phase (M) hanges into ciliated colum ar pithelium (R) H—E 160

T P MAE

Fig 67 The lower margin of the perforation, 2.1 mm anteriorly to the level of Figs 62—64. The squamous epithelium immigrates onto the tympanal side, especially subepithelially (up to 1.0 mm). Superficially the squamous epithelium changes into [illegible] metaplastic type (arrows), and after [illegible] short distance cilia are seen on the surface. (MAE = meatus ac. ext. P = perforation edge, T = tympanum.) H—E 4 [illegible] x.

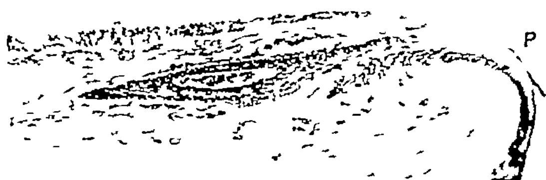


Fig 68 Epithelial immigration and the area of epithelial change seen in Fig 67 ([illegible] from the perforation edge). Tympanally, extreme left, the only sign of metaplasia [illegible] is a slight basal [illegible] of ciliated epithelium. The subepithelial projection shows no keratin or granular cells. ([illegible] = perforation edge.) H—E 160

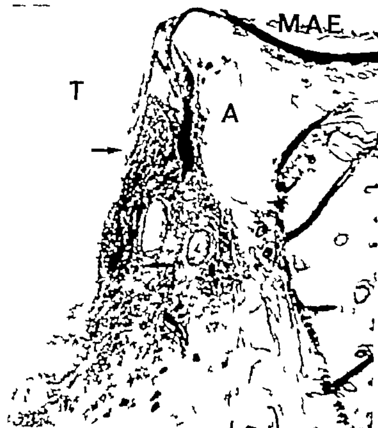


Fig 65 The lower margin of the perforation, 0.2 mm anteriorly to the level of Figs. 62—64 Superficial and subepithelial ingrowth of epidermis is seen The keratin characteristics continue almost to the junction (upper arrow) The hypotympanal stroma is loose and oedematous. Subepithelial follicular lymphocyte infiltration can be seen (lower arrow) (A = annulus memb tymp., T = tympanum, MAE = meatus acust.) H—E 40 x

Fig 66 The epithelial transitional area seen also in Fig 65 (from the upper arrow downwards) The epidermis (E) after a short (up to 1.0 mm) squamous *metaplastic phase* (M), changes to ciliated columnar epithelium (R) H—E 160 x

Fig 67 The lower margin of the perforation, 2.1 mm anteriorly to the level of Figs 62—64. The squamous epithelium immigrates onto the tympanal side, especially subepithelially (up to 1.0 mm). Superficially the squamous epithelium changes into metaplastic type (arrows), and after short distance cilia are seen on the surface. (*MAE = meatus ac. ext. P = perforation edge, T = tympanum*) *H– E 40*

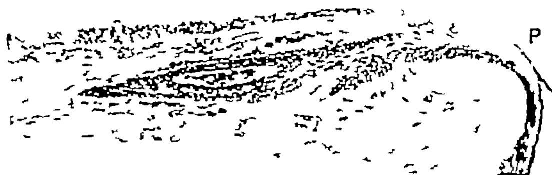


Fig 68 Epithelial immigration and the area of epithelial change seen in Fig 67 (tympanally from the perforation edge). Tympanally extreme left, the only sign of metaplasia visible is slight basal hyperplasia in ciliated epithelium. The subepithelial projection shows no keratin or granular *cells* (*P* = perforation edge) *H—E 160*

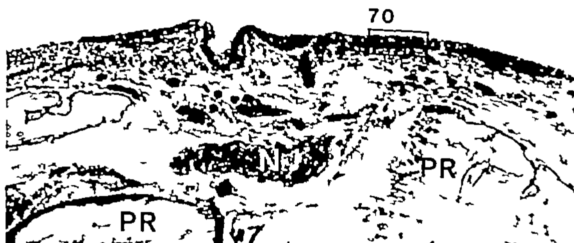


Fig 69 Metaplastic epithelium of the anterior promontory (PR = promontory NJ = nervus Jacobson.) H—E 40 x.



Fig 70 An area of metaplastic epithelium in Fig 69 (square 70) Basal hyperplasia is distinct cilia are absent, and stratification is slight There is no stratum spinosum. H—E 400



Fig 71 Epithelium from the medial tympanal wall, 1.3 mm anteriorly to the level of Fig 69 Basal hyperplasia increased eosinophilia and disorganization of cells underneath the cilia, indicating early metaplasia, are seen H—E 400 x.

surface and the other laterally to the hypotympanum. In the anterior tympanum the medial wall was partly covered by meta plastic (independent? metaplasia) epithelium (Figs. 69—71). Antero-inferiorly it was connected to the lateral metaplastic (junction metaplasia) and squamous epithelium.

In the orifice of the Eustachian tube the mucous membrane was covered by typical ciliated columnar epithelium containing numerous basophilic secreting cells and goblet cells.

All keratin stains were consistent with the squamous epithelial immigration seen in the H E stain. Thus in the inferior margin, keratinizing squamous epithelium was seen, at a maximum, 1 0 mm on the tympanal side. In the ossicular area, the granular cell layer and overlying keratin disappeared at the umbo level The other tympanal epithelium showed no keratin-positivity

Tubal and the mucous tympanal epithelium was AB- and PAS-positive (also some ciliated cells) The columnar cells showed most intensive staining in their apical parts. Epidermis was AB- and PAS-negative strongly metaplastic epithelium was AB-negative but faintly PAS-positive. In the areas of slight metaplasia the superficial cells stained also weakly with AB.

4 9 TEMPORAL BONE 9

This patient had died at the age of 70 of bilateral bronchopneumonia. Otoscopically her right ear showed a large perforation of the pars tensa which was marginal in the infero-posterior quadrant. On macroscopic examination the tympanic mucosa was slightly thicker than normal but there was no discharge in the ear canal.

4 9 1 *Histology*

The perforation in the pars tensa measured 3 1 mm vertically and 4.8 mm horizontally The remaining pars tensa was considerably thicker than normal, measuring 0.2—0.3 mm, and showed changes typical of tympanosclerosis. Epidermis from the external side of the drum remnants grew over the perforation edges to the tympanal side (Figs. 72—77). This extension varied, so that at the superior margin the squamous epithelium extended up to 1.3 mm, at the inferior margin up to 1.7 mm and at the anterior margin up to 0 4 mm tympanally At the posterior margin, epidermis ended at the perforation edge. The change of the squamous epithelium into tympanic flat, cuboidal or even ciliated epithelium was abrupt (Figs. 73—79) At certain areas, the thick keratinizing squamous epithelium and the stratified columnar ciliated epithelium were side by side (Fig. 78) At the inferior area, the keratinizing squamous epithelium partly covered the hypotympanic stroma but, here as well, ended abruptly in a junction with the flat and thin cuboidal epithelium (Figs. 75—77). Postero-inferiorly the squamous immigration extended even to the medial wall of the tympanum. Thus the immigration seemed to take place more easily over this marginal area. When the squamous epithelium formed a junction with the tympanic epithelium on the tympanosclerotic tissue on the upper part of the drum, the tympanal epithelium resembled

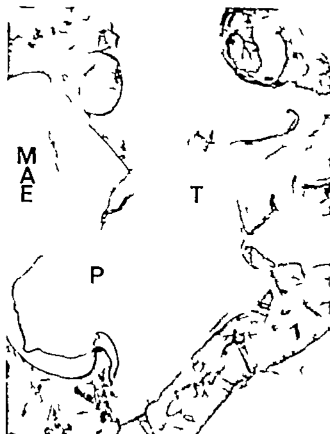


Fig 72 General view of the tympanum. The ear canal (MAE), ear drum perforation (P) and middle ear space (T) is seen the section level passing just posteriorly to the level of the windows. There is no active inflammatory process. Figs. 73—77 are closer views of details in the same section. H—E.

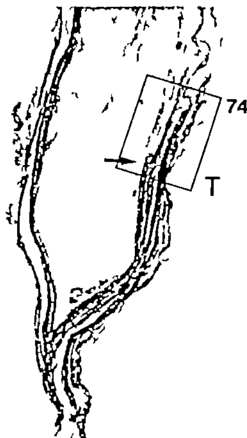


Fig 73 (bottom left). The upper margin of the perforation also seen in Fig 72. The epidermis, with all its layers, immigrates onto the tympanal side (T) terminating abruptly (arrow) The ear drum remnant is tympanosclerotic. H—E 40 x.



Fig 74 (bottom right) The epidermal junction on the tympanal side of the perforation edge seen also in Fig. 73 (square 74) The epidermis with its strata changes abruptly into flat epithelium. The epidermis is slightly hyperkeratotic. The underlying stroma is tympanosclerotic. H—E 160 x



Fig. 75. The lower margin of the perforation in Fig 2. The epidermis immigrates onto the tympanal side (T) with all its cell layers, and terminates abruptly in flat epithelium. H—E 40.



Fig. 76. The epidermal junction in the infero-lateral angle of the tympanum in Fig. 75. Immigrating epidermis, with its layers, terminates abruptly and changes, over an endothelial phase of ca. 0.1 mm, into ciliated epithelium. H—E 100.

Fig. 77. The junction in Fig. 76. Stratum corneum, stratum granulosum, stratum spinosum and stratum basale clearly distinguishable up to the junction. The subepithelial stroma is loose and oedematous. H—E 400 x.

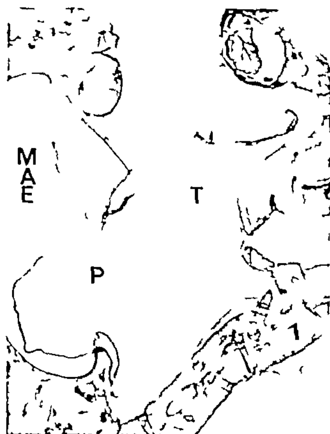
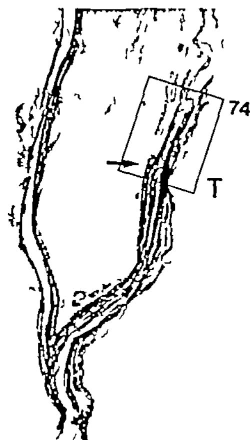
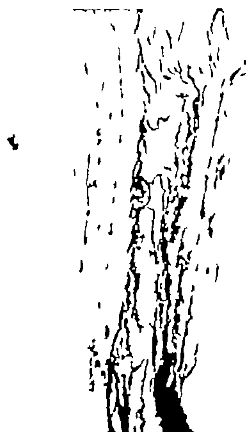


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endothelium but the junction was nevertheless sharply defined (Figs. 73 74)

Loose sheets of keratin were seen in the tympanic cavity close to the perforation. They covered the medial side of the perforation edges and partly the hypotympanic mucosa corresponding to the area of immigrating epidermis. The keratin stains demonstrated distinct phospholipid granules in the granular cell layer which ended slightly before or at the front of the advancing squamous epithelium. There was no sign of any collection of keratin debris in the middle ear and the degree of keratinization was that of the ear canal epidermis.

The promontory was covered by fibrotic 0.05—0.2 mm thick mucosa. Superiorly the promontorial epithelium was low cuboidal, or flat endothelial. Opposite to the perforation and at the inferior tympanum it changed to cuboidal epithelium with 2 or 3 cell layers. At the posterior part of the tympanum, the subepithelial tissue became thinner and was covered by a thin cuboidal or flat endothelium-like epithelium of 1—2 cell layers. In the hypotympanum, some of the epithelial cells were ciliated. Malleus, incus and stapes were intact.

In the anterior tympanum, epithelium consisted generally of 3—5 cell layers and was cuboidal without cilia. At the orifice of the Eustachian tube, and in the tube itself the epithelium had 3—10 cell layers showing in places, here as well as in the anterior tympanum, basal hyperplasia. Ciliated cells were seen particularly at the inferior areas from which ciliated narrow epithelial strips continued to the inferior tympanum and even to the posterior tympanum. In other areas ciliated cells were scarce. A few secreting cells were seen, mainly in the lateral part of the tympanal tube.

The keratin stains were consistent with the H E stain showing the immigrating squamous epithelium in the process of keratinization (and epidermal in character) up to the sharp junction with the tympanal columnar cuboidal or flat epithelium. The mucus stains were faintly positive in the Eustachian tube epithelium the tympanal area was almost devoid of positively staining epithelial cells.

4.10 TEMPORAL BONE 10

The patient's medical history is given under Temporal Bone 8. Otoscopy revealed a total perforation of the right pars tensa. The malleus handle was missing, and the ear was moist.

4.10.1 *Histology*

A fibrotic annular remnant was all that was left of the pars tensa (Fig. 80). At the postero-inferior perforation edge the epidermis extended, showing some signs of parakeratosis, over the region of the annulus, up to 0.5 mm to the tympanic side. In the hypotympanum this squamous epithelium became metaplastic (Fig. 81) and further on columnar in some places even ciliated. Elsewhere along the perforation edges the ear canal epidermis was transformed at the annular level into metaplastic epithelium, which lost its squamous character after at the most, 0.5 mm on the tympanic side of the annulus (Figs. 82—84).

The promontory was lined by metaplastic epithelium (Fig. 85), which encircled a 1.5 mm high and 2 mm wide area of squamous



Fig 78 The squamo-columnar junction in the infero-medial p[illegible] of the posterior tympanum. The epidermis (E) with its lay[illegible] changes abruptly into ciliated columnar (R) and further [illegible] cuboidal (Cu) and flat, endothelial epithelium (F). At the ju[illegible]tion, the epidermis seems to grow over the columnar epithel[illegible] (for up to 0.15 mm) H—E 100 x.

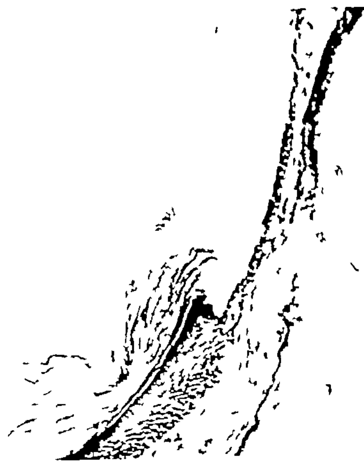


Fig 79 The [illegible]re correspond[illegible]ng to Fig 78 but 0 4 mm a[illegible]teriorl[illegible] The ep[illegible]thelial change is [illegible]ery abrupt. H—E 100



Fig 82 An area in Fig 80 In the upper annular region the epidermis loses its stratum granulosum (arrow) on the ear canal side H—E 160



Fig 83 An area in Fig 80. In the upper annular region, just on the ear canal side, the squamous epithelium terminates abruptly and continues as metaplastic epithelium H—E 160



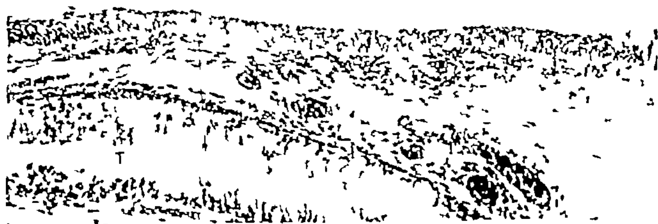
Fig 84 The upper annular region (A) in Fig 80 The epithelium has 2—3 cell layers and resembles squamous epithelium in appearance No different types of cell layers are distinguishable H—E 160



Fig 85 An area in Fig 80 The metaplastic epithelium (M) seen at the top of this figure is distinctly transformed into the squamous type (at about the middle of the promontory), with a prominent basement membrane The stroma is relatively fibrotic H—E 160

Fig 80 General view of the tympanum. The perforation is marginal, the mucous membrane of the tympanum thick, hyperaemic and oedematous. Figures 81—87 are details of the areas marked with corresponding numbers and arrows. (T = tympanum, PR = promontory A = remnants of annulus membranae tympanicus) H—E.

Fig 81 An area in Fig 80. The left margin of the figure coincides with the inferior annular remnant. The squamous epithelium (SQ) had prickles and superficial keratin-positive material but there is no granular cell layer. Tympanally (right) the squamous epithelium continues, showing a decreasing degree of metaplasia. The basement membrane area is prominent. Subepithelially there is a pouch (T) connected with the middle ear space and lined by respiratory epithelium. H—E. 160 ×.



epithelium (independent metaplasia). In this squamous epithelium (Fig. 86) the basal cells formed a distinct layer of their own. Prickle cells were seen, the stratum granulosum was absent, and pseudoparakeratosis was seen over a small area. This squamous epithelium (Fig. 87) was inferiorly connected to the ear canal epidermis by slightly metaplastic epithelium. The connection, however was so narrow and the connecting metaplastic epithelium of such a low grade that the squamous epithelium on the promontory is likely to be of independent metaplastic origin.

The posterior tympanic floor and almost all the posterior tympanum were lined by a higher columnar epithelium which had undergone a mucous change. In the anterior tympanum the epithelium was ciliated and metaplastic, relatively thick, in the medial wall up to 10 cell layers (basal hyperplasia). Anteriorly to the perforation level a medial, a lateral and an inferior area of metaplasia could be distinguished. Posteriorly these areas united and at the level of the anterior edge of the annulus, they formed an unbroken lining that covered the lowest two-thirds of the lateral wall, the tympanic floor and the entire medial wall. The metaplasia was most pronounced medially and least pronounced in the floor where it began to weaken from the anterior tympanum backward. At the level of the posterior part of the promontory the metaplastic epithelium changed into columnar mucous epithelium. The epithelium of the epitympanum was less continuous, partly mucously changed and columnar and in the posterior parts of the middle ear it became more eosinophil cuboidal, and 1—2 layered.

The respiratory type epithelium of the orifice of the Eustachian tube was extensively hyperplastic. Some goblet and secretory cells were seen. The tubotympanal unbroken ciliary carpet continued backwards as an infero-medial strip extending to the sinus tympani and as a second, considerably shorter strip to the infero-lateral parts of the tympanum.

The tympanic mucosa, which was heavily thickened throughout, was hyperaemic and oedematous Only in the centre of the promontorial area and in the region of the lower perforation edge was it more fibrotic. Mainly subepithelially there was extensive, essentially lymphocytic infiltration. The malleus handle, the long process of incus, and the superstructure of the stapes were absent (Fig. 80).

No keratin-positive cells were found in the squamous epithelium of the promontory The tendency to keratinization of the squamous epithelium at the postero-inferior edge of the perforation, disclosed by the H E staining, was also confirmed by keratin stainings.

The tympanic epithelium stained well with both AB and PAS methods. The metaplastic epithelium, and the squamous epithelium of the perforation edges and the promontory stained with PAS, especially in their upper parts. AB staining, on the other hand, produced a slight positive response only in the area of the slightly metaplastic epithelium.

4 11 TEMPORAL BONE 11

The patient, at 83 had died in a chest hospital of acute respiratory infection complicating bilateral bronchiectatic disease. His hearing had been poor since childhood and the ears had shown intermittent discharge. Otoscopically the right ear showed total marginal

Fig 86 An area in Fig. 80, down from the Fig 85 area. Pseudoparakeratotic squamous epithelium is visible on the promontorial surface. Its stratum basale is distinct, stratum granulosum absent, but prickles can be discerned. H—E 400 x

Fig 87 An area also seen in Fig 80, down from the Fig 86 area. The pseudoparakeratotic squamous epithelium changes into less markedly metaplastic epithelium. H—E 160 x.



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4 11 TEMPORAL BONE 11

The patient, at 83 had died in a chest hospital of acute respiratory infection complicating bilateral bronchiectatic disease. His hearing had been poor since childhood and the ears had shown intermittent discharge. Otoscopically the right ear showed total marginal

Fig 87 A area also seen in Fig 80, down from the Fig 86 area. The pseudo-pa akeratotic squamous epi thelium changes into less markedly metaplastic epithelium. H—E 160 x.



Fig 86 A area in Fig 80, dow from the Fig 85 area. Pseudoparakeratotic squamous ep thel um is isibl on the promontorial surface Its strat m bas le is distinct, stratum gra losum absent, but prickles can be discerned H—E 400 x.

epithelium (independent metaplasia). In this squamous epithelium (Fig. 86) the basal cells formed a distinct layer of their own. Prickle cells were seen, the stratum granulosum was absent, and pseudoparakeratosis was seen over a small area. This squamous epithelium (Fig. 87) was inferiorly connected to the ear canal epidermis by slightly metaplastic epithelium. The connection, however, was so narrow and the connecting metaplastic epithelium of such a low grade that the squamous epithelium on the promontory is likely to be of independent metaplastic origin.

The posterior tympanic floor and almost all the posterior tympanum were lined by a higher columnar epithelium which had undergone a mucous change. In the anterior tympanum the epithelium was ciliated and metaplastic, relatively thick, in the medial wall up to 10 cell layers (basal hyperplasia). Anteriorly to the perforation level, a medial, a lateral and an inferior area of metaplasia could be distinguished. Posteriorly these areas united and at the level of the anterior edge of the annulus, they formed an unbroken lining that covered the lowest two-thirds of the lateral wall, the tympanic floor and the entire medial wall. The metaplasia was most pronounced medially and least pronounced in the floor where it began to weaken from the anterior tympanum backward. At the level of the posterior part of the promontory the metaplastic epithelium changed into columnar mucous epithelium. The epithelium of the epitympanum was less continuous, partly mucously changed and columnar and in the posterior parts of the middle ear it became more eosinophil, cuboidal, and 1—2 layered.

The respiratory-type epithelium of the orifice of the Eustachian tube was extensively hyperplastic. Some goblet and secretory cells were seen. The tubotympanal, unbroken ciliary carpet continued backwards as an infero-medial strip extending to the sinus tympani and as a second, considerably shorter strip to the infero-lateral parts of the tympanum.

The tympanic mucosa, which was heavily thickened throughout, was hyperaemic and oedematous. Only in the centre of the promontorial area and in the region of the lower perforation edge was it more fibrotic. Mainly subepithelially there was extensive, essentially lymphocytic infiltration. The malleus handle, the long process of incus, and the superstructure of the stapes were absent (Fig. 80).

No keratin-positive cells were found in the squamous epithelium of the promontory. The tendency to keratinization of the squamous epithelium at the postero-inferior edge of the perforation, disclosed by the H.E. staining, was also confirmed by keratin stainings.

The tympanic epithelium stained well with both AB and PAS methods. The metaplastic epithelium, and the squamous epithelium of the perforation edges and the promontory stained with PAS, especially in their upper parts. AB staining, on the other hand, produced a slight positive response only in the area of the slightly metaplastic epithelium.

4.11 TEMPORAL BONE 11

The patient, at 83, had died in a chest hospital of acute respiratory infection complicating bilateral bronchiectatic disease. His hearing had been poor since childhood and the ears had shown intermittent discharge. Otoscopically the right ear showed total marginal

Fig 86 An area in Fig 80, down from the Fig 85 area. Pseudoparakeratotic squamous epithelium is visible on the promontorial su f ce Its stratum basal is disti ct, stratum granulosum absent, but prickles can be discerned H—E 400

Fig 87 An area also seen in Fig. 80, down from the Fig. 86 area. The pseudoparakeratotic squamous epithelium changes into less markedly metaplast c epithelium. H—E 160 x.





Fig. 90 The superior squamo-columnar junction in Fig. 88 (arrow 90). The epidermis (E) also projects through granulation tissue superomedially. N.B. the strong stratum granulosum, marked keratinous scaling (K), and abrupt epithelial junctions (arrows). H–E 40 x.

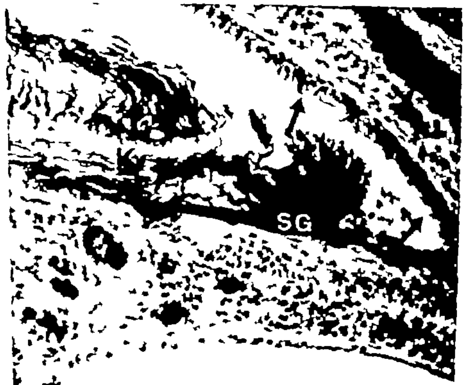


Fig. 91 Details of the abrupt change of squamous into tympanal epithelium, also seen in Fig. 90. Ciliated cells (arrow) are seen almost immediately after the junction (SG = stratum granulosum, K = keratin.) H–E 100

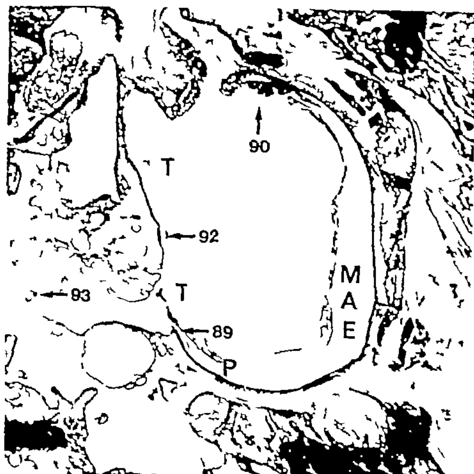


Fig 88 General view of the tympanum, immediately posteriorly to the promontorial level. The perforation is marginal at this level, and the epidermis immigrates smoothly over the (inferior) annular remnant. (MAE = meatus ac. ext., T = tympanum, P = perforation level) H–E.



Fig 89 The immigrating epidermis in the infero-lateral part of the tympanum (T) in Fig 88 (arrow 89), changes into columnar epithelium. At the junction, there is a short sliding as squamous epithelium pushes off the tympanal epithelium from its base (arrow). H–E 160 ×.



Fig 94 Metaplastic epithelium of the medial tympanal wall, 0.6 mm anteriorly to the Fig 88 level. In some places there is transformation into squamous epithelium (arrows). The promontorial connective tissue is thick and fibrous. H—E 40 x.



Fig 95 Infero-medial wall of the anterior tympanum. The mucous membrane is highly *hyperplastic*. The epithelium is stratified, loose and hyperplastic. Subepithelially there are numerous glandular structures and, more peripherally, large number of cysts. H—E 40



Fig 92 The squamous epithelial islet in the posterior promontorial surface in Fig 88 (arrow 92). There were prickles but no stratum granulosum. Pseudoparakeratotic scaling is seen on epithelial surface (M = metaplastic squamous epithelium) H—E 160 x.



Fig 93 The isolated squamous epithelial islet in the sinus tympani, seen in Fig 88 (arrow 93) Stratum basale stratum spinosum and stratum granulosum are distinguishable The most superficial cells appear to be shed into the lumen The islet is surrounded by loose cuboidal epithelium. There are granulocytes in the lumen. The basement membrane area is distinct. H—E 160 x.



Fig. 98 The upper perforation edge in Fig. 96 (arrow 98). Up to the abrupt junction, the epidermis shows pronounced stratum granulosum and marked keratinization. At the junction, the squamous epithelium pushes the tympanal epithelium off its base (arrow). Cilia were noted the distance of few tenths of millimetres from the junction. H—E 160

Fig. 97 An inferior area of the posterior tympanum in Fig. 96 (arrow 97). The epidermis is gradually losing its characteristics and is transformed, through the phases of para (P) and pseudoparakeratosis (Ps), into metaplastic squamous epithelium (M), and finally into respiratory type epithelium (R). The total breadth of area covered by the figure is 1 0 mm, and the distance from the right margin to the annular level is 0 5 mm H—E 120 x.



Fig 96 General view of the tympanum 15 mm posteriorly to the Fig 8 level. (MAE = meatus ac ext., T = tympanum, P = perforation level) H—E.





Fig. 98 The upper perforation edge in Fig. 96 (arrow 98). Up to the abrupt junction, the epidermis shows a pronounced stratum granulosum and marked keratinization. At the junction, the squamous epithelium pushes the tympanal epithelium off its base (arrow). Cilia were noted at the distance of a few tenths of millimetres from the junction. H—E 160 x.

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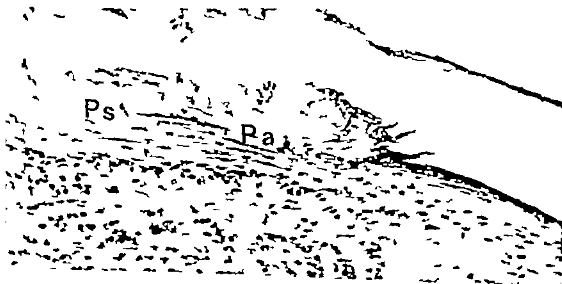


Fig 99 The upper perforation edge correspond ng to F g. 98, 0.6 mm anteriorly The stratum gra ulosum of the immigrating, partly parakerototic epidermis is very prom nent. The epithelial junction is abrupt (arrow) H—E 160 x.



F g 100 0 2 mm posterio ly to the Fig 88 level. The hypotympanal immigrati g squamous ep thelium in trudes derneath th cuboidal/columna ep theli m of the middl ear (shd g) See lso Figs. 89 and ee H—E 256

perforation of the pars tensa. The middle ear was moist but the ear canal had no noticeable discharge.

4.11.1 *Histology*

Inferiorly a tiny fibrous annulus remained, and the ear canal epidermis grew smoothly over it on the hypotympanic mucosa and continued, tapering, medially (Figs. 88, 96, 97). Both posteriorly and anteriorly to this area the squamous ear canal epithelium immigrated less extensively into the hypotympanum, but always for a distance of at least 0.5 mm. At the anterior and superior edge of the perforation the squamous epithelium showed a tendency to penetrate the inflamed tissue to the epitympanic space where a keratinizing squamous epithelium was seen to grow for a distance of 0.5 mm on the epitympanal mucosa (Figs. 90, 91). At the superior edge the squamous epithelium grew along the adhesion bridges over the remaining parts of the ossicles towards the medial wall of the middle ear. In certain areas the propria under the squamous epithelium was thin and fibrotic, in others it was oedematous and loose, infiltrated by inflammatory cells and, especially anteriorly by numerous gland-like structures and cysts (Fig. 95).

Generally keratinizing squamous epithelium changed into columnar or ciliated columnar epithelium for a very short distance (Figs. 89, 98—100), sometimes through a metaplastic transitional area (Fig. 97). In some places in the hypotympanum the squamous epithelium tended to grow beneath the columnar epithelium for a short distance, pushing it aside (Figs. 98, 100). The granular cell layer and the superficial keratin followed the squamous epithelium close to the point of epithelial junction. In the hypotympanic area, a parakeratotic desquamation was sometimes seen.

In the tympanum, the squamous epithelium was always smooth and showed no papillary growth. The main part of the promontorial epithelium was metaplastic, and lacked the granular cell and keratin layers (Fig. 94). On the posterior promontory this metaplasia surrounded an area of squamous epithelium 1.8 mm high and 0.8 mm wide (Fig. 92) connected with a very narrow squamous strip to immigrating ear canal epithelium. This independent promontorial squamous epithelium showed prickles and some granular cells. The cell layers, however were not yet distinctly arranged and some pseudoparakeratotic desquamating strips could be seen on top of the epithelium.

An isolated area of squamous epithelium was found in the sinus tympani, which was otherwise covered by the columnar type of epithelium (Figs. 88, 93). This squamous epithelium showed basal, prickle, and granular cell layers. There was no superficial keratin but some of the external cells were seen loose in the lumen in a parakeratotic fashion.

Generally the tympanic mucosa was very hyperplastic, fairly hyperaemic and infiltrated by chronic inflammatory cells. The cariotic ossicular chain was surrounded and fixed by fibrotic tissue. The head of the malleus showed a bony union to the roof of the epitympanum.

In the anterior part of the tympanum the columnar epithelium contained large ciliated areas which decreased in number posteriorly. However in the lower tympanum, ciliated narrow strips continued to the most infero-posterior parts. Also some areas of the medial wall and the superior portion of the tympanum showed ciliated cells.

The orifice of the Eustachian tube showed a thick mucosa which was oedematous and infiltrated with inflammatory cells. The tubal epithelium was ciliated columnar with stratified and pseudostratified arrangement of cells.

The immigrating squamous epithelium gave a positive response to keratin staining whereas the metaplastic and the promontorial columnar epithelium were negative.

Fig 99 The upper perforation edge corresponding to Fig 98, 0.6 mm anteriorly The stratum granulosum of the immigrating, partly parakeratotic epidermis is very prominent. The epithelial junction is abrupt (arrow) H—E 160 x.

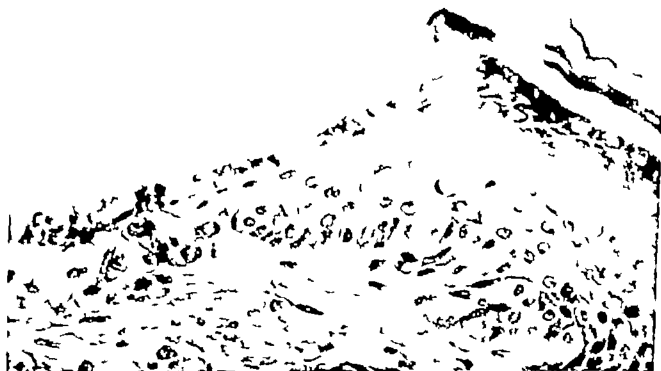


Fig 100 0.2 mm posteriorly t the Fig 88 le l The hypotympanal immigrating squamous epithelium intrudes underneath the cuboidal/col m ar epithelium of the middle ear (sliding) See also Figs 89 and 98 H—E 256

perforation of the pars tensa. The middle ear was moist but the ear canal had no noticeable discharge.

4.11.1 *Histology*

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The orifice of the Eustachian tube showed a thick mucosa which was oedematous and infiltrated with inflammatory cells. The tubal epithelium was ciliated columnar with stratified and pseudostratified arrangement of cells.

The immigrating squamous epithelium gave a positive response to keratin stainings whereas the metaplastic and the promontorial squamous epithelium were negative.

Tubal and tympanal epithelium was AB and PAS-positive. Tympanally medial metaplastic epithelium also stained with both methods, whereas the squamous epithelium was AB negative and very faintly PAS-positive

4 12 TEMPORAL BONE 12

The patient's medical history is given under Temporal Bone 11 Otoscopy revealed a total marginal perforation of the left pars tensa There was purulent discharge in the ear canal

4 12 1 *Histology*

The drum membrane showed a large perforation which comprised the whole pars tensa and the anterior part of Shrapnell's membrane. The epidermis of the ear canal immigrated both inferiorly and superiorly (Figs. 101—103) onto the middle ear forming at the posterior promontory a relatively strongly keratinizing unbroken lining of squamous epithelium This lining continued about 1 mm backward The sinus tympani was free from squamous epithelium and was covered by metaplastic and ciliated columnar epithelium Hypotympanally the epidermal immigration gradually withdrew in a lateral direction extending in the posterior part of the perforation only to the area of the annular remnant Towards the antero-inferior edge of the perforation the change was similar On the other hand the superior squamous epithelial immigration which began from the anterior part of the perforation and at the oval window level extended along the bridge formed through the ossicular chain to line the medial wall retained its dimension in the following sections (backward) and joined the inferior epidermal ingrowth at the level described at the beginning of this chapter Anteriorly of the long process of the incus, the connective tissue bridge was interrupted by a short air space in the medial part of the epitympanum The fairly strongly keratinizing squamous epithelium also immigrated to this air space and lined its lower part, and after a short slightly metaplastic transitional area it changed abruptly into cuboidal epithelium of 1—3 layers (Fig 104)

No appreciable squamous epithelial immigration was noted in the anterior and posterior perforation edge

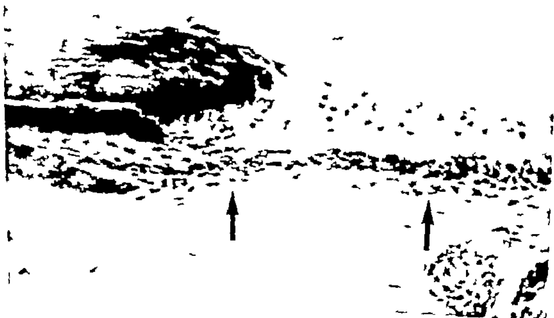
At some places of the perforation edges, the squamous epithelium sent projections (Figs. 105—107) into the subepithelial connective tissue. The tendency to depth growth was particularly evident medially of the upper edge of the perforation where it was epitympanally directed (Figs. 105 106) In addition a few small subepithelial keratin cysts could be seen in the medial tympanal wall under the immigrated epidermis.

In general the epidermal junctions with other epithelium were fairly sharp often strongly keratinizing epidermis extended with all its layers right up to the line of junction and was transformed through a weak metaplastic phase of varying length into cuboidal or columnar epithelium In places the immigrating epidermis lost its keratin and granular layer a few tenths of millimetres before the junction It was



Fig 101 General view of the tympanum Inferiorly the squamous epithelium immigrates directly into the hypotympanum (nothing is left of the perforation edge), superiorly the immigration takes place along bridge formed by the carotic auditory ossicles The head of the malleus shows bony union to the epitympanic roof Above the cholesterol cyst (CC), in the lower part of the epitympanal cavity there is an area of hyperkeratotic epidermis (arrow). H—E.

Fig 102 The hypotympanal squamo-columnar junction in Fig 101 (arrow 102). At the abrupt junction line the partly parakeratotic epidermis thickens and its granular cell and keratin layers are very pronounced Beyond the transition zone of some 0.2 mm (between arrows) the epithelium is respiratory and showed also ciliary coating the right margin of the figure *H—E 160*



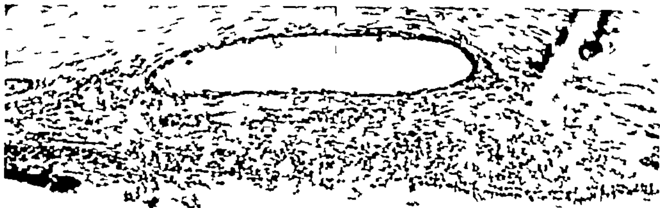


Fig 103 The squamo-columnar junction on the tympanal side of the upper perforation edge (2.9 mm anteriorly to the level of Fig 101) The epidermis is abruptly changed into columnar epithelium of [illegible]atery appearance and is soon covered by cilia. H—E 160 x

Fig 104 Medial wall of the tympanum in the oval window area. The immigrating aggressive-looking epidermis keratinizes abundantly (K = keratin) and stratum granulosum is prominent. The epithelial junction is abrupt (arrow). H—E 160 x.



Fig. 105. General view 1.9 mm anteriorly to Fig. 101. A nearly total epidermization (= epidermal covering) is seen, being absent only from the oval window (O) area. The epidermis shows a tendency to depth growth towards the attic (arrow) superiorly and at the perforation level area (arrow) inferiorly. A cholesterol cyst (CC) is seen in the oval window area. (A = anular level.) H—E.



Fig. 106. The superior area seen in Fig. 105 (arrow 106). The immigrating, aggressive, cholesteatomatous epidermis show atticial depth growth, acanthosis (Ak), hyperkeratosis and prominent stratum granulosum (K = keratin.) H—E ×0 x.



Fig. 107. The inferior anular area seen in Fig. 105 (arrow 107). The ear canal epidermis sends a subepithelial projection (arrow) to the tympanal direction. H—E 40.

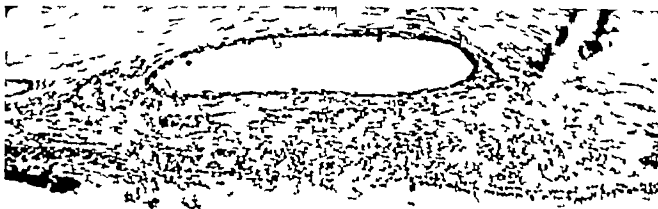


Fig. 103 The squamo-columnar junction on the tympanal side of the upper perforation edge (2.9 mm anteriorly to the level of Fig. 101). The epidermis is abruptly changed into columnar epithelium of watery appearance and is soon covered by cilia. H—E 160 x.

Fig. 104 Medial wall of the tympanum in the oval window area. The immigrating eggwhite-looking epidermis keratinizes abundantly (K = keratin), and stratum granulosum is prominent. The epithelial junction is abrupt (arrow). H—E 160

4.13 TEMPORAL BONE 13

This patient had died at the age of 58 of bronchial carcinoma with extensive metastases. Otoscopy of his left ear drum revealed a nearly total marginal perforation. The ear contained some purulent exudate.

4.13.1 *Histology*

The pars tensa of the drum membrane was totally absent. Shrapnell's membrane was replaced by connective tissue obliteration, forming a bridge from the level of the ear canal roof through the ossicular remnants to the oval window area. At the level of the anterior promontory the obliteration completely blocked the connection up- and forward from the mesotympanum (Fig. 108). The malleus handle was missing.

The epidermis of the ear canal completely lined the anterior part of the tympanic cavity. The promontory also was totally epidermized. Posteriorly the keratinizing squamous epithelium gradually began to disappear beginning at the posterior oval window area. The floor of the tympanum, however, was almost completely lined by epidermis. In the posterior parts of the perforation the epidermal immigration was considerably slighter and extended only a short distance onto the tympanic side. In the junctional areas, 0.1—0.5 mm before the epidermis ended, it was seen to lose the keratin cover, the stratum granulosum and gradually also the stratum spinosum, and through a parakeratotic (and a pseudoparakeratotic) phase it was transformed into metaplastic and gradually into columnar epithelium (Figs. 109, 110). The total width of the area of transformations varied, but was usually of the order of 1—2 mm. At some places in the area the epithelium was low, of a clearly squamous type, non-keratinizing and —3 layers thick.

All epidermal cell layers could be distinguished in the normally keratinizing squamous epithelium of the middle ear (Figs. 111, 112). Extensive perinuclear vacuolization was typical (Fig. 109) apart from the most basal cell layers. Furthermore, the epidermal papillary structure was absent from the tympanic side. Moderate keratin film, seen throughout on the squamous epithelium, nowhere formed an accumulation suggestive of incipient cholesteatoma. Nor was any subepithelial growth of the tympanic squamous epithelium noted.

The mucosa, free from squamous epithelium, of the postero-medial wall of the tympanum, sinus tympani and the postero-medial side of the luminal roof was lined by columnar epithelium which was partly detached. No cilia were seen. Profuse infiltration of inflammatory cells and strong hyperaemia in the subepithelial connective tissue were observed in these areas. At the junctions towards the squamous epithelium this stroma, which throughout the middle ear was strongly thickened, became poor in cells, denser and less vascularized. In the pouches the mucosa was looser and cysts and pseudocysts were visible.

The epithelium of the Eustachian tube was of the respiratory type, and in some places hyperplastic. Cilia lined its surface throughout (Fig. 114). The tubal lumen opened into the anterior tympanum after which, posteriorly, the cavity diminished and ended blindly. In the anterior tympanum, the epithelium, mainly superiorly and inferiorly, changed from respiratory into cuboidal (Fig. 113), partly also losing its ciliary lining. Laterally a strip of cilia continued to the postero-lateral angle of the cavity. The anterior tympanum and especially the tube contained goblet cells and large numbers of secretory columnar cells.

Keratin stainings confirmed the epidermal keratinizing character of the squamous epithelium of the middle ear (Fig. 112).

In mucus stainings the superficial parts of the tympanic squamous epithelium were faintly positive to PAS but not at all to AB.

typical of the junctional areas, however that the borderline was very sharp and an epi dermis of aggressive appearance often "clashed with a remarkably delicate type of epithelial cells

Posteriorly the promontory was lined by strongly keratinizing squamous epithelium Anteriorly the medial wall epithelium was metaplastic (disorganized, multilayered non squamous) and the frontal part was even ciliated with basal hyperplasia. Considerable amounts of keratin were seen on the surface of all squamous epithelium with an unin terrupted connection with the ear canal Only in the lower part of the epitympanal cavity was there some keratin collection on the squamous epithelium suggesting incipient cholesteatoma.

In the posterior tympanum the epithelium was uncontinuous and of columnar and cuboidal type, with occasional cilia on its surface. In the anterior tympanal area it was also uncontinuous stratified and partly lined by cilia. The watery appearance was typical of this modified respiratory epithelium and this made the exact evaluation of the epithelium difficult.

Already anteriorly the luminal roof and the medial wall showed changes suggestive of early epithelial metaplasia. In the anterior tympanum the roof first lost the ciliation which continued posteriorly as medial and supero-lateral tapering strips for some 2 mm The markedly broad inferior track of ciliated cells continued on the tympanic floor and further infero-medially to the posterior parts of the tympanum At the level of the win dows the strip was interrupted by the zone of squamous epithelium described above

The epithelium of the Eustachian tube was respiratory somewhat hyperplastic and remarkably watery It was lined by cilia throughout only at the tubal orifice the roof epithelium had no cilia.

The tympanic mucosa especially in the anterior parts and the pouches, was heavily thickened and oedematous There were numerous cysts and pseudocysts, and some gland like structures, mainly in the medial wall of the tympanum (Fig 105) Polypotic granulation formation was seen in the antero-inferior part of the medial wall Generally the promontorial mucosa, especially in the posterior parts, was more fibrotic and less infiltrated by inflammatory cells. A cholesterol cyst was seen in the upper part of the oval window area, between the facial canal and the incudostapedial joint. The malleus handle was missing and its cariotic head showed a bony union to the roof of the epitympanum (Fig 101)

The tympanic squamous epithelium showed strong keratin staining The granular cell layer stained with both the Baker and the Ladewig method giving a pronounced dark and red line, respectively in which individual granules of varying size could be discerned only here and there Keratin staining seemed more pronounced on the tympanic than the ear canal side

The columnar cuboidal secretory and mucously changed epithelium of the Eustachian tube and tympanum stained with AB and more markedly with PAS The tympanic squamous epithelium stained faintly with PAS, mainly in its superficial parts. This epithelium as well as the area of marked metaplasia, were AB negative,



Fig. 109. The junction of the superior squamous immigration in Fig. 108 (arrow 109). The basal epithelial layers are hyperplastic and perinuclear vacuolization is seen more superficially. Stratum granulosum ends (arrow), and there is no keratin film. The fibrotic subepithelium becomes looser and is infiltrated abundantly by round cells on reaching the area of columnar epithelium. H—E 160.



Fig. 110. The junction of the inferior squamous immigration (on the upper promontory surface) in Fig. 108 (arrow 110). The epidermis is seen to lose the granular cells after a parakeratotic phase (Pa) and to change through pseudoparakeratosis (Ps) into squamous epithelium of metaplastic type (M), and further into columnar epithelium (R). The basement membrane area is distinctly seen under the squamous epithelium. A stromal reaction begins in the junctional area and becomes pronounced towards and under the columnar epithelium. The width of the area covered by Fig. 110 is less than 1.0 mm. H—E 160 x.

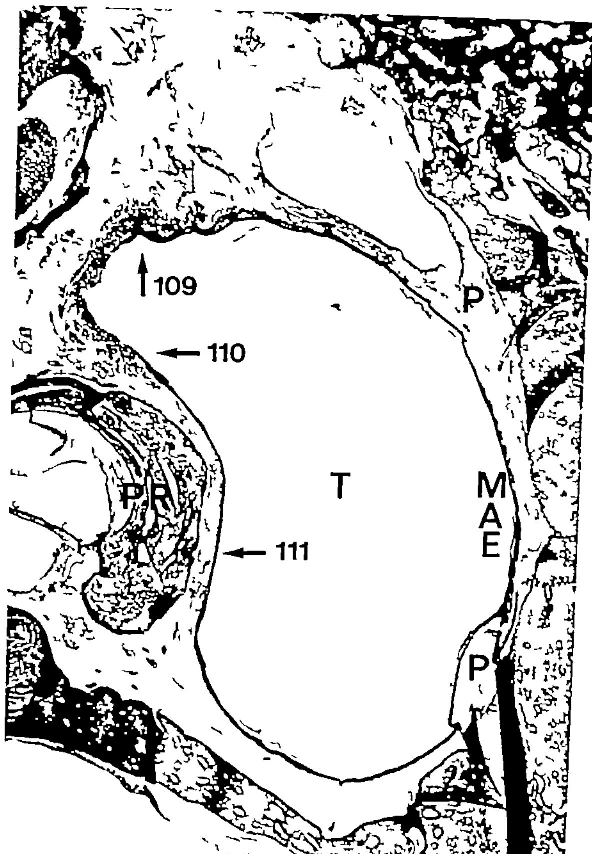


Fig 108 General view of the tympanum The section l el is th t f the windows I this figure the perforation is total The tympanum is almost throughout lined by keratinizing stratified squamous epithelium erlying f brotic connecti tissu I he o l window area the squamous epith li m is repla ed by columna epithelium whi h was largely detached and under which profuse inflammatory c ll infiltration in loose subepithelial stroma is seen (MAE = meatus xt T = tympanum, PR = promontory P = perforation les L) H—E



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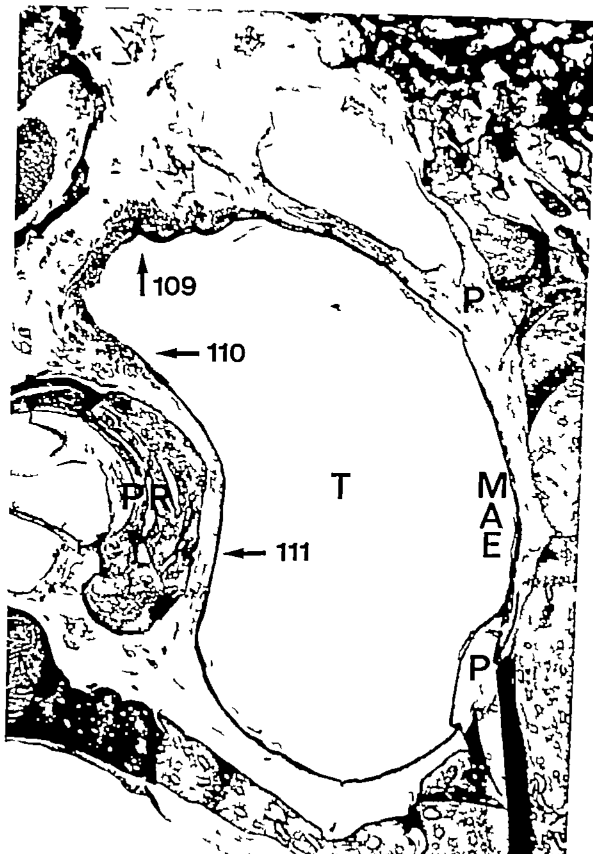


Fig 108 General vi w of the tympanum The section l l is th t of th windows In this figure, the perforation is total The tympanum is lmost throughout lined by k ratinizing stratified squamous ep thelium erlying fibrotic connecti tissue I the ov l w ndow rea the *squamous epithel um is replaced by columnar epithel um which was larg ly detached* nd under which profuse inflammatory c ll infiltration in loose subepithelial stroma is seen (MAE = meatus ac ext T = tympanum, PR = promontory P = perforation le L) H—E.

Fig 113 From the upper part of the anterior tympanum Flat cuboidal epithelium carries cilia H—E 160 x.

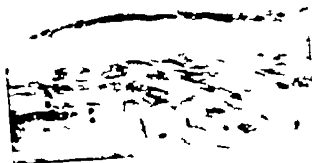


Fig 114 I fero-medial epithelial boring of he re- bot mpanal are T goblet ll with secre- tory olumnar cell between them re seen The type of he epithelium is pseu dostratified, ciliated and column H—F 800 (This microphotogr ph taken by he immersion echnique)



Fig 111 Epidermal surface of the promontory in Fig. 108 (arrow 111) All epidermal layers can be clearly distinguished. H—E 400 x.



Fig 112 Promontorial epidermis in Baker staining (corresponding to the area of Fig. 111). The stratum granulosum (arrow) and the keratin cover are clearly distinguishable (dark colour) with this phospholipid staining H—E 256

Fig 113 From the upper part of the anterior tympanum Flat cuboidal epithelium carries cilia H—E 160



Fig 114 [illegible] fero medial epithelial lining of the [illegible] hypotympanal re [illegible] T goblet [illegible] with secre tory columnar cell between them are seen The type of the epithelium is pseudo stratified, ciliated and columnar H—E 800 (This microphotograph is taken by the immersion technique)

Table 1 *A synopsis of the findings described in Chapter 4*

Only positive findings* are noted.

Temporal Bone	1	2	3	4	5	6	7	8	9	10	11	12	13
Age	85	56	70	59	59	11	70	51	70	51	83	83	58
Duration of ear symptoms	deaf	40 yrs	for years	minimum 4 months	minimum 4 months	1 year	?	from childhood	?	from childhood	from childhood	from childhood	?
Total absence of drum													
Total defect of pars tensa										+	+	+	+
Subtotal defect of pars tensa								+	+				
Central perforation	+	+	+	+	+	+	+						
Dry tympanum									+				
Moist tympanum						+				+	+		
Purulent tympanum	+	+	+	+	+		+	+				+	+
Epidermosis												±	
Hyperkeratosis									±			+	
Squamous immigration	+	+	+	+	+	(+)		+	+	+	+(+)	++	++
Epidermal implantation											+		
Eversion						+	+						
Squamous metaplasia	+	+	+	+	+	±	+	+	±	+	+	+	+
— Junction metaplasia	+	+	+	+	+		(+)	+		+	+	+	+
— Independent metaplasia (basal hyperplasia)		+		+		±	(+)	+	±				
— Independent squamous metaplasia (stratification/prickles)			+	±						+	+		
— Independent squamous metaplasia with prickles										+	+		
— Squamous metaplasia with keratin or str. granul.													
— Promontorial metaplasia			+	+		±		+		+	+		
— — Slight metaplasia (basal hyperplasia)				+		±		+					
— — Squamous metaplasia (stratification/prickles)			+	±						+	+		
Breadth (mm) of the transitional area in squamous immigration	0—0.3	0.5?	ad 1.0	0.1—0.2	0.5—1.0	(0)		0.1—1.0	0	0.5—1.0	0—0.5	0.1—0.3	ca. 1—2.0
Depth growth in transitional areas of squamous immigration				+	+	++	+	+				(+)	

…emporal Bone	1	2	3	4	5	6	7	8	9	10	11	12	13
…anthosis (+) or depth growth (++) in the epidermis … the …mular … of Shrapnell membrane					+	±	+	+		+	++	++	
…r ae …n (mm) of squamous penetration	0—2.0	0—2.0	0—1.0	0—0.3	0—2.0(PR)	(0—1.0)		1.0	ad 1.7	ad 0.5	0.5—1.0(PR?)	not (ad PR)	ad PR
…quamous epithelium thickened …e junction							+		±		±	+	+
…rominent basement membrane at …e junction				±						+			
…olding							+		±		±		
…Bridge of adhesion to medial …mpanic wall		+			+			+			+	+	+
– superiorly (through adhesion …cles)		+			+			+			±	+	+
– inferiorly					+						+		
…flammatory cell infiltration in …e tympanum	+	+	+	+	+	+	+	+		+	+	+	+ (not under sq. epith.)
…flammatory cell infiltration, …pecially at the (squamo-colum…ar) junction	±			±				+		±		±	
…flammatory cell infiltration in …e …ar …nal stroma close to …ar …um	±	+	+	±	+			±		+			
…ollicular lymphocyte accumulations in the tympanum						+	+	+		+	+	+	
…ula in the tympanum (number of strips)	+ (4)	±	+ (3)	+ (3)	+ (2)	+ (2)	+ (2—3)	+ (2)	+ (1)	+ (2)	+ (3)	+ (3)	+ (1)
…ecretory cells in the tympanum	±	±	±	±	+	±	+	+		+	+	+	+
…luid in the tympanum					+		+	+		+	++	++	
…ysts in the tympanum	+	+	+	+	+	+	+	+	+	+	+	+	+
…ympanosclerosis				±					+				

++ = strongly positive finding, + = positive finding, ± = weak or indefinite finding, (+) = finding equivalent to positive finding.

PR = promontory

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Subtotal defect of p rs t sa								+	+				
Central perforation	+	+	+	+	+	+	+						
Dry tympanum									+				
Moist tympanum						+				+	+		
Purulent tympanum	+	+	+	+	+		+	+				+	+
Epidermosis												±	
Hyperk tosis									±			+	
Squamous imm gration	+	+	+	+	+	(+)		+	+	+	+(+)	++	++
Epidermal implantation											+		
E rosion						+	+						
Squamous metaplasia	+	+	+	+	+	±	+	+	±	+	+	+	+
— Junction metapl si	+	+	+	+	+		(+)	+		+	+	+	+
— Independent metaplasia (basal hyperplasia)		+		+		±	(+)	+	±				
— Independent squamous metaplasia (stratification/prickles)			+	±						+	+		
— Independent squamous metaplasia with prickles										+	+		
— Squamous metaplas with k ratin or st gran l													
— Promontorial metaplasia			+	+		±		+		+	+		
— — Slight metapl ia (basal hyperplasia)				+		±		+					
— — Squamous m taplasia (stratification/prickles)			+	±						+	+		
Breadth (mm) of the transitional area i squamous imm gration	0 2—0 3	0 5?	ad 1 0	0 1—0 2	0.5—1 0	(0)		0.1—1.0	0	0 5—1.0	0 —0.5	0 1—0.3	ca. 1—2 0
Depth growth n transitional areas of squamous immigration				+	+	++	+	+				(+)	

Temporal bone	1	2	3	4	5	6	7	8	9	10	11	12	13
Acanthosis (+) or depth growth (++) in the epidermis the ...ular re of the pars ... membrane					+	±	+	+		+	++	++	
Extent (mm) of squamous immigration	0—2.0	0—0	0—1.0	0—0.3	0—2.0(PR)	(0—1.0)		1.0	ad 1.7	d 0.5	0.5—1.0(PR?)	not (ad PR)	d PR
Squamous epithelium thickened at the junction							+		±		±	+	+
Prominent basement membrane at the junction				±						+			
Sl[illegible]							+		±		±		
Bridge of adhesion — medial tympanic wall		+			+			+			+	+	+
— superiorly (through auditory ossicles)		+			+			+			±	+	+
— inferiorly					+						+		
Inflammatory cell infiltration in the tympanum	+	+	+	+	+	+	+	+		+	+	+	+ (not under sq. epith.)
Inflammatory cell infiltration, especially at the (squamo-columnar) junctions	±			±				+		±		±	
Inflammatory cell infiltration in the basal stroma close to drum	±	+	+	±	+			±		+			
Follicular lymphocyte accumulations in the tympanum						+	+	+		+	+	+	
Cilia in the tympanum (number of strips)	+ (4)	±	+ (3)	+ (3)	+ (2)	+ (2)	+ (2—3)	+ (2)	+ (1)	+ (2)	+ (3)	+ (3)	+ (1)
Secretory cells in the tympanum	±	±	±	±	+	±	+	+		+	+	+	+
Glands in the tympanum					+		+	+		+	++	++	
Cysts in the tympanum	+	+	+	+	+	+	+	+	+	+	+	+	+
Tympanosclerosis				±					+				

++ = strongly positive finding, + = positive finding, ± = weak or indefinite finding, (+) = finding equivalent to a positive finding.

PR = promontory

5 DISCUSSION

5 1 POSTMORTEM CHANGES AND ARTIFACTS

Hentzer (1969) after fixation more than three hours post mortem found autolytic structural damage in the cell organelles, e g the cilia In his study (1970) of normal middle ear mucosa, he therefore used immediate post mortem fixation He also omitted the decalcification and he attributed the remarkably extensive tympanic ciliation to the better preserving power of this technique. Sadé (1966 a) when he described the extensive ciliary lining of the middle ear characteristic of the true mucosa used immediate postmortem fixation and a short decalcification period. In their light and electron microscopic studies Lim et al (1967) Kawabata & Paparella (1969) Lim & Hussl (1969) Hussl & Lim (1969 a, b) and Lim (1970) also used techniques omitting decalcification As pointed out by Hentzer (1970) it is evident that both a too late postmortem fixation and the long term decalcification with strong acids, which have been used earlier damaged the epithelial lining and especially the cilia, leading to misinterpretations. Differences in interpretation can also be attributed to improved staining methods and increased interest in the mucociliary system and the mechanism of secretory otitis.

Since postmortem autolytic changes begin in the first few hours after death it is obvious that such changes are present in ears which have been stored for an average of 58 hours, although cold storage prevents pronounced autolysis. The relatively long period of decalcification (6—8 weeks) also affects the architecture of epithelial cells. Despite the fact that including intermediate storages, it took 3—11 months before the sections were completed the distortions of cell and tissue structure were slight and did not hamper the microscopic analysis With the present method the cilia were well preserved, and appeared as an almost unbroken carpet in the Eustachian tubes of all ears. Nor could any correlation be noted between the preservation on the tympanal cilia and the various durations (13—91 hours) of the pre-fixation cold storage periods. Since the cilia are structures very sensitive to damage, it can be assumed that autolysis and possible preparation artifacts play no remarkable role in the present work

5 2 VALIDITY OF STAININGS

In addition to the H E staining for general characteristics, PAS and AB stains were used mainly to give information on the epithelial secretory function and mucin composition Since the diastase digestion in PAS staining was not used the polysaccharides (e.g glycogen) if present also gave a positive reaction

In the normal epidermis, phospholipids are found in the granular cell layer where the epithelial cells begin to keratinize The quality of the resulting keratin depends on the degree of hydrolysis of the transitional zone as hydrolytic enzymes are liberated from lysosomes (Jarrett & Spearman 1967) Phospholipids rich in energy are formed at the time of nuclear breakdown and their energy is needed when polypeptide chains are re-synthetized and polymerized into a keratin molecule (Jarrett et al 1959) The phospholipid content of the horny layer indicates the

degree of autolysis of the transitional zone: if the autolysis is effective, phospholipids are seen in the transitional zone only but if the hydrolysis is defective the whole cell including the nucleus, travels into the horny layer which is then positively stained for phospholipids (Jarrett et al 1965)

The turquoise-bluish colour imparted by Luxol Fast Blue to keratinizing areas was often relatively faint, but the morphology of the epithelial cells was clearly visualized with this staining

Baker's method stained the phospholipid positive areas blue-black throughout, and was the best and most informative of the keratin staining methods used. In addition to the phospholipoproteins, also e.g. the nucleoproteins stain with Baker's method. For this reason, only negative Baker staining after phospholipid extraction confirms the (phospholipid-) specificity of this staining method. Extraction can be carried out e.g. by lipase digestion with pyridine extraction, the results are uncertain (T Palva et al 1972) Since formalin fixation makes the phospholipoprotein complex resistant to the lipase effect, digestion should have been carried out on fresh unfixed sections. With the present study plan, this was impossible. The corresponding controls have been carried out on frozen sections (T Palva et al., 1972) and they showed that positive epidermal staining was due to phospholipids.

The Ayoub-Shklar modification of Mallory's staining usually stained the whole epithelium red, and the keratin selectivity claimed by Shklar (1968) was not visible in the formalin-fixed sections. For this reason this staining was replaced with Ladewig's modification, which stained the keratin layer and granules an intense reddish violet. T Palva et al. (1972) assumed that a fixation artefact was involved here also, for no similar staining could be verified in unfixed frozen section staining.

The keratin stainings together supplied so much information of keratinization that tympanic keratinization process findings seen on H E staining, and confirmed by the keratin stainings used, can be considered reliable.

5.3 PATHOLOGY OF THE TYMPANUM AND TYMPANIC MEMBRANE

(See also Table I on pp 86,87)

5.3.1 *Types of perforation*

The present material contained seven central perforations of the pars tensa two were partly marginal (= subtotal) and four total. In ears with total perforation of the pars tensa, the epitympanum was extensively obliterated by connective tissue and the pars flaccida was replaced by thick fibrotic obliteration in the region of the auditory ossicles. In three of these ears (Temporal Bones 11—13) a bridge developed, running along the ossicular chain to the medial wall of the middle ear However none of the four showed the typical attic perforation, nor were there any signs of epitympanal lateral bone erosion. The handle of the malleus had in all four cases been destroyed.

Of the perforations of the present material, one was dry (Temporal Bone 9), three were moist (Temporal Bones 6, 10, 11), and the remaining nine were suppurative.

The absence of attic perforation and cholesteatoma in the present material deserves special attention (one ear Temporal Bone 12 showed however "aggressive" hyperkeratosis). A total of 900 ears were inspected to collect the present material and, if the four ears with adhesive processes not included in the material are taken into account, the number of chronic middle ear processes found was 17 (1 9 per cent). There were also three ears which had been treated with radical mastoidectomy and when they are included the incidence rises to 2.2 per cent. On school age material, Ostman (1902) quoted an incidence of 1.6, Lergard (19.3) 1 4 and Marland (1918) 6 9 per cent. Bezold (1891) found

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Since postmortem autolytic changes begin in the first few hours after death it is obvious that such changes are present in ears which have been stored for an average of 58 hours, although cold storage prevents pronounced autolysis The relatively long period of decalcification (6—8 weeks) also affects the architecture of epithelial cells Despite the fact that, including intermediate storages, it took 3—11 months before the sections were completed the distortions of cell and tissue structure were slight and did not hamper the microscopic analysis. With the present method the cilia were well preserved, and appeared as an almost unbroken carpet in the Eustachian tubes of all ears. Nor could any correlation be noted between the preservation on the tympanal cilia and the various durations (13—91 hours) of the pre-fixation cold storage periods. Since the cilia are structures very sensitive to damage, it can be assumed that autolysis and possible preparation artifacts play no remarkable role in the present work

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cuboidal and even flat epithelium of a few ears.

The ciliated columnar epithelium of an active hyperplastic mucosa was occasionally up to 5—10 cell layers thick. Cuboidal and flat epithelium appeared more often on the fibrotic mucous membranes, free from inflammatory cells e.g. in Temporal Bone 9 the cuboidal and flat, even endothelium-like epithelium predominated. These findings support the view that inflammation stimulus produces epithelial hypertrophy (Ojala, 1950) and, especially in chronic infections, hyperplasia and metaplasia (Zechner 1965). According to Friedmann (1959), chronic inflammation causes the reversal of flat epithelium to respiratory type. After inflammation and trophic hyperaemia have disappeared, atrophy again resulting in flat type epithelium takes place (Ojala, 1950).

5.3.3.2. Mucous epithelium and secretory components

The amount of epithelium showing varying degree of mucous change was considerable in about half of the ears. It was most abundant in Temporal Bones 7 and 8 which showed extensive epithelial areas composed almost solely of goblet cells.

In addition to the goblet cells, also columnar and cuboidal secretory cells were seen. Even some ciliated cells showed PAS- and AB-positive material which may suggest a possible secretory function (Sadé, 1966 a). The apical parts of the epithelial cells reacted best to mucus stainings. Glands were noted in six ears, the largest numbers in Temporal Bones 11 and 12. Cysts were visible in all. Both the glandular and the cystic secretion was AB- and PAS-positive. The secretory (mainly goblet) cells were absent from three ears, but even in them, apart from Temporal Bone 9 the epithelium in some places showed PAS-positive and, more faintly AB-positive staining. In Temporal Bone 9 only a few cystic cavities stained PAS- and AB-positively.

It is generally accepted that hyperplastic transformation (Sadé, 1966 b) and increased secretory function of the epithelium (Wittmaack, 1918 Beck, 1926 Singer 1933 Friedmann, 1956 Bendek, 1963 T Palva et al., 1964 Zechner 1965) result from chronic inflammation. But it is not clear whether in this connection a basal cell on differentiation becomes a secretory and not a ciliated cell (Rhodin, 1959), or whether a ciliated cell undergoes metaplasia into a goblet cell (Spoendlin, 1959) The former mechanism has had more supporters (Latta & Schall, 1934 Lim et al., 1967) In secretory otitis, Lim & Birck (1971) found electron microscopically ciliogenesis in some cells containing secretory granules. This might indicate that the cells were adapting themselves to the transport needs increased by secretory otitis. Since in secretory otitis the epithelium shows a hyperplastic transformation, a proliferation rather than a metaplasia (Lim & Birck, 1971), it does not seem meaningful for a secretory cell population to develop through a highly specialized ciliary cell phase engaged in transport function. It is more probable that the secretory cells differentiate and proliferate directly from the basal cells. The fact that some young ciliating cells show secretory granules is no direct evidence against the above mechanism. Nor can far reaching conclusions be drawn on the basis of the electron microscopic architecture of a few cells. On the other hand, if a certain differentiation of the basal cell begins in a phase of profuse proliferation it may remain partial, and result in the above intermediate forms. The AB- and PAS-positivity of some ciliated cells also may instead of secretory function, indicate an active carbohydrate metabolism of the ciliated cells, e.g. PAS-positivity (without diastase) may show glycogen (as a source of cell energy) The possibility of artifacts and the *partial differentiation*, mentioned above, also must be taken into consideration in

a cholesteatoma and/or perforation of Shrapnell s membrane in 14 6 per cent of his cases of chronic otitis Accordingly the present material should have contained three cases of this type Considering that Scheibe (1917) found a cholesteatoma in 91 and Simpson (1954) in 94 per cent of their cases of chronic otitis with epitympanal perforation, it may be assumed that treatment has been sought earlier for ears with cholesteatomatous and at the same time, often attical processes. In fact, three operated cases were included in the present total material

5.3.2 *Mucosal quality*

The tympanic mucosa in all the cases was thickened to a varying extent. Not only mucosal hyperplasia of varying degree but in places also very pronounced oedema, and in some cases marked organization, fibrosis and even tympanosclerosis (Temporal Bone 9) was seen. Granulation processes of different degrees were noted. There were varying numbers of cysts and pseudocysts, and glands were seen in six ears they usually stained positively both with AB and PAS Vascularization varied, but was usually abundant.

In 12 temporal bones the tympanal mucosa was infiltrated by inflammatory cells to a varying extent The predominant types of cells were lymphocytes and plasma cells. Polymorphonuclear cells were also seen in a few ears Varying numbers of macrophages were observed. In Temporal Bone 9 the mucosa was the most fibrotic of the whole material and the active inflammatory process was over It was also the only completely dry ear of the material

The subepithelial round cell infiltration formed follicular accumulations in six ears (cf Goerke, 1905 Wittmaack, 1926 Singer 1933 T Palva et al 1964) One patient (Temporal Bones 11 12) had a history of tuberculosis in the lymph nodes of the neck, and another (Temporal Bones 8 10) had been treated in a chest hospital for pulmonary tuberculosis. The follicles however showed nothing suggestive of tuberculosis but apparently represented a mode of reaction typical of the middle ear mucosa in prolonged, chronic inflammation According to Singer (1933) inflammatory cell infiltration acts as the reticuloendothelial system of middle ear mucosa. These cell accumulations may participate in local antibody formation (Zechner 1966)

Squamo-columnar epithelial junctions, in particular were infiltrated by inflammatory cells only once (Temporal Bone 8) In three ears a few lymphocytes were seen under the squamous epithelium up to the junction but *from the junction onward their number* increased (Temporal Bones 11— 13) and even follicular formations appeared (Temporal Bones 11 12) This finding supported the general impression that the round cell infiltration underneath the squamous epithelium was somewhat less pronounced than under the columnar cuboidal or flat epithelium.

5 3.3 *Epithelium*

5.3.3 1 Columnar cuboidal and flat epithelium

Respiratory epithelium was very common in the middle ear Cilia were seen in all the cases, and they usually continued backward from the unbroken ciliary lining of the orifice of the Eustachian tube and antero-inferior tympanum as one to four tapering tracks. In most temporal bones they remained within the maximal extension limits defined by Sadé (1966 a) but sometimes exceeded them (Hentzer 1970) in the posterior tympanum and epitympanum and even in the region of mastoid air cells (T Palva et al., 1964) Cilia were also occasionally seen on the tympanic surface of the ear drum (e g Temporal Bone 6) In one ear (Temporal Bone 7) the myringitic ear drum was tympanally lined by ciliated columnar epithelium which everted onto its external side In addition to columnar epithelium cilia appeared at some places on the

cuboidal and even flat epithelium of a few ears.

The ciliated columnar epithelium of an active hyperplastic mucosa was occasionally up to 5—10 cell layers thick. Cuboidal and flat epithelium appeared more often on the fibrotic mucous membranes, free from inflammatory cells e.g. in Temporal Bone 9 the cuboidal and flat, even endothelium-like epithelium predominated. These findings support the view that inflammation stimulus produces epithelial hypertrophy (Ojala, 1950) and, especially in chronic infections, hyperplasia and metaplasia (Zechner 1965). According to Friedmann (1959), chronic inflammation causes the reversal of flat epithelium to respiratory type. After inflammation and trophic hyperaemia have disappeared, atrophy again resulting in flat-type epithelium takes place (Ojala, 1950).

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The tympanic mucosa in all the cases was thickened to a varying extent Not only mucosal hyperplasia of varying degree but in places also very pronounced oedema and in some cases marked organization fibrosis and even tympanosclerosis (Temporal Bone 9) was seen Granulation processes of different degrees were noted. There were varying numbers of cysts and pseudocysts, and glands were seen in six ears they usually stained positively both with AB and PAS Vascularization varied but was usually abundant.

In 12 temporal bones the tympanal mucosa was infiltrated by inflammatory cells to a varying extent. The predominant types of cells were lymphocytes and plasma cells Polymorphonuclear cells were also seen in a few ears. Varying numbers of macrophages were observed In Temporal Bone 9 the mucosa was the most fibrotic of the whole material and the active inflammatory process was over It was also the only completely dry ear of the material

The subepithelial round cell infiltration formed follicular accumulations in six ears (cf Goerke, 1905 Wittmaack 1926 Singer 1933 T Palva et al., 1964) One patient (Temporal Bones 11 12) had a history of tuberculosis in the lymph nodes of the neck, and another (Temporal Bones 8 10) had been treated in a chest hospital for pulmonary tuberculosis. The follicles however showed nothing suggestive of tuberculosis but apparently represented a mode of reaction typical of the middle ear mucosa in prolonged, chronic inflammation According to Singer (1933) inflammatory cell infiltration acts as the reticuloendothelial system of middle ear mucosa. These cell accumulations may participat in local antibody formation (Zechner 1966)

Squamo-columnar epithelial junctions, in particular were infiltrated by inflammatory cells only once (Temporal Bone 8) In three ears a few lymphocytes were seen under the squamous epithelium up to the junction but from the junction onward their number increased (Temporal Bones 11— 13) and even follicular formations appeared (Temporal Bones 11 12) This finding supported the general impression that the round cell infiltration *underneath the squamous epithelium* was somewhat less pronounced than under the columnar cuboidal or flat epithelium.

5.3.3 *Epithelium*

5 3.3 1 Columnar cuboidal and flat epithelium

Respiratory epithelium was very common in the middle ear Cilia were seen in all the cases, and they usually continued backward from the unbroken ciliary lining of the orifice of the Eustachian tube and antero-inferior tympanum as one to four tapering tracks. In most temporal bones they remained within the maximal extension limits defined by Sadé (1966 a) but sometimes exceeded them (Hentzer 1970) in the posterior tympanum and epitympanum and even in the region of mastoid air cells (*T Palva et al., 1964*) Cilia were also occasionally seen on the tympanic surface of the ear drum (e g Temporal Bone 6) In one ear (Temporal Bone 7) the myringitic ear drum was tympanally lined by ciliated columnar epithelium which everted onto its external side. In addition to columnar epithelium cilia appeared at some places on the

cuboidal and even flat epithelium of a few ears.

The ciliated columnar epithelium of an active hyperplastic mucosa was occasionally up to 5—10 cell layers thick. Cuboidal and flat epithelium appeared more often on the fibrotic mucous membranes, free from inflammatory cells e.g in Temporal Bone 9 the cuboidal and flat, even endothelium like epithelium predominated. These findings support the view that inflammation stimulus produces epithelial hypertrophy (Ojala, 1950) and, especially in chronic infections, hyperplasia and metaplasia (Zechner 1965) According to Friedmann (1959), chronic inflammation causes the reversal of flat epithelium to respiratory type. After inflammation and trophic hyperaemia have disappeared, atrophy again resulting in flat type epithelium takes place (Ojala, 1950)

5332. Mucous epithelium and secretory components

The amount of epithelium showing varying degree of mucous change was considerable in about half of the ears. It was most abundant in Temporal Bones 7 and 8 which showed extensive epithelial areas composed almost solely of goblet cells.

In addition to the goblet cells, also columnar and cuboidal secretory cells were seen. Even some ciliated cells showed PAS- and AB-positive material which may suggest a possible secretory function (Sadé, 1966 a). The apical parts of the epithelial cells reacted best to mucus stainings. Glands were noted in six ears, the largest numbers in Temporal Bones 11 and 12. Cysts were visible in all. Both the glandular and the cystic secretion was AB- and PAS-positive. The secretory (mainly goblet) cells were absent from three ears, but even in them, apart from Temporal Bone 9 the epithelium in some places showed PAS-positive and, more faintly AB-positive staining. In Temporal Bone 9 only a few cystic cavities stained PAS- and AB-positively

It is generally accepted that hyperplastic transformation (Sadé, 1966 b) and increased secretory function of the epithelium (Wittmaack, 1918 Beck, 1926 Singer 1933 Friedmann, 1956 Bendek, 1963 T Palva et al., 1964 Zechner 1965) result from chronic inflammation. But it is not clear whether in this connection a basal cell on differentiation becomes a secretory and not a ciliated cell (Rhodin, 1959) or whether a ciliated cell undergoes metaplasia into a goblet cell (Spoendlin, 1959). The former mechanism has had more supporters (Latta & Schall, 1934 Lim et al., 1967) In secretory otitis, Lim & Birck (1971) found electron microscopically ciliogenesis in some cells containing secretory granules. This might indicate that the cells were adapting themselves to the transport needs increased by secretory otitis. Since in secretory otitis the epithelium shows a hyperplastic transformation, a proliferation rather than a metaplasia (Lim & Birck, 1971) it does not seem meaningful for a secretory cell population to develop through a highly specialized ciliary cell phase engaged in transport function. It is more probable that the secretory cells differentiate and proliferate directly from the basal cells. The fact that some young ciliating cells show secretory granules is no direct evidence against the above mechanism. Nor can far reaching conclusions be drawn on the basis of the electron microscopic architecture of a few cells. On the other hand, if a certain differentiation of the basal cell begins in a phase of profuse proliferation it may remain partial, and result in the above intermediate forms. The AB- and PAS-positivity of some ciliated cells also may instead of secretory function, indicate an active carbohydrate metabolism of the ciliated cells, e.g. PAS-positivity (without diastase) may show glycogen (as a source of cell energy). The possibility of artifacts and the partial differentiation, mentioned above, also must be taken into consideration in

those cases. But it must be said, however that if the cell stains positively both with AB and PAS it is most likely to produce mucous secretion

5.3.3.3 Metaplastic epithelium

Metaplasia in this connection refers to a change of the normal epithelial type, at the site concerned toward some other type There is squamous epithelial metaplasia but also e.g respiratory and glandular meta plasia Changes of respiratory epithelium leading to metaplastic squamous epithelium can be classified as follows (Auerbach et al 1956)

Stage 1 Basal cell *hyperplasia.* The stratum basale undergoes hyperplasia and becomes several layers thick However the over lying (ciliated) columnar epithelium is still present.

Stage 2 Stratification. The superficial cells are flattened and columnar cells have disappeared. Other characteristics of squa mous epithelium are not yet visible

Stage 3 Metaplastic squamous epithelium The cells of the superficial layers resemble prickle cells with intercellular bridges

In the present study signs of incipient metaplasia on the tympanic epithelium were interpreted to consist of hyperplasia, in creased eosinophilia (in H E) disorganiza tion of cells and nuclei and condensation of cytoplasm These changes correspond mainly to Stage 1 but include also cases originating at a lower epithelium than the respiratory type.

Two kinds of metaplasia could be dis cerned in the tympanum (1) independent metaplasia of tympanic epithelium and (2) metaplastic epithelium at the junction of tym panic epithelium and the squamous epithelium in continuity with immigrating ear canal epidermis The latter is often a kind of transitional area between squamous and tympanic epithelium.

Metaplasia at least of a slight degree in one or both of the above forms was seen in all ears of the present material although in two ears the finding was slight and uncertain (Temporal Bones 6 9). Distinct independent metaplasia was seen in six ears (and uncertain findings in Temporal Bones 6, 7 9). Junction metaplasia was seen in 11 ears.

5.3.3.3 1 Independent metaplasia

In three ears the change remained at the stage of basal hyperplasia, in one ear at the stage of stratification and in two ears (both involving a moist total perforation of the pars tensa) prickles were seen as indication of true metaplastic squamous epithelium *No keratin or granular cell layer* was seen In these two cases (Temporal Bones 10 11) there was pseudoparakera totic scaling of the metaplastic squamous epithelium which covered a relatively fibrotic *promontorial connective tissue. In two* uncertain cases (Temporal Bones 6, 9) the degree of metaplasia was so low that not even a true basal hyperplasia could be noted The only changes seen were a *slightly increased number of cell layers, and* disorganization of epithelial cells. In one case (Temporal Bone 7) basal hyperplasia was localized along the margins of the per foration on the ear canal side, beneath the everted columnar epithelium, the thickness of the basal cell layer varying from 2—3 to over 10 cells. In six of these nine ears metaplasia was seen on the promontorial mucosa All cases of stratification or true squamosity (*Auerbach s 2nd and 3rd stages*) belonged to this group

5 3 3.3.2 Junction metaplasia

Junction metaplasia was noted in 11 ears In six of them independent *metaplasia was* also recorded In one ear the squamo-columnar junction was so abrupt throughout, that no metaplastic zone of transition could be seen The epidermis with all its layers, ended *abruptly and sometimes* the very next cell was a flat endothelium-like cell (Tem

poral Bone 9 Fig. 77) Furthermore, in one ear (Temporal Bone 6) the squamous epithelium at the perforation edge grew into the ear drum stroma but not onto the tympanic surface, and therefore there could be no junction metaplasia (Figs. 49 50) In all the other ears with immigration there was a transitional area of varying width, although sometimes in the same ear clear cut junctions at different levels and different sites of the perforation could be seen in addition to junction metaplasia. The width of junction metaplasia ranged from 0.1 to 2 0 mm, average 0.5 mm.

Junction metaplasia cannot be described by the various degrees of metaplasia, as can independent metaplasia. The epithelial change was often gradual and the evident squamous-type epithelium still belonged to the immigration process. Junction metaplasia, on the other hand, referred to the less thick and often relatively simple "junctional epithelium which could not yet be classified as post-immigration tympanic nor any longer as squamous epithelium. A longer stretch of pseudoparakeratotically scaling junction metaplasia with prickle cells was seen in one ear (Temporal Bone 12), and a *mainly* stratification-type change in two ears (Temporal Bones 8, 10).

Inflammation of the ear canal contiguous to the ear drum, and epithelial immigration were seen in seven of the 11 ears with junction metaplasia. In three ears (Temporal Bones 11—13) with junction metaplasia and pronounced immigration, the ear canal skin near the drum had already healed and become fibrotic The fourth ear with immigration but free from ear canal inflammation was the only dry ear (Temporal Bone 9)

5.3.3.4 Immigrating squamous epithelium

The middle ear epidermis and squamous epithelium which are in continuity with the ear canal epidermis are here called immigrating. Any tympanic epidermis found in the material was always continuous, with the epidermis of the ear canal or ear drum covering varying distances from perforation edges towards the tympanum There was no case in the material of epidermis occurring solitarily in the tympanum, except one implantation islet in Temporal Bone 11 without continuity to the ear canal and/or ear drum epidermis. The conclusion to be drawn is that any epidermis seen tympanally is a result of epidermal ingrowth.

Immigrating squamous epithelium was seen in all cases, except Temporal Bone 7 with the epithelial eversion (emigration) Depth growth of squamous epithelium, primarily on junction areas, was seen in five ears, and in one of them (Temporal Bone 6) the immigration only took the form of a subepithelial squamous projection into the tympanic side of ear drum stroma. Also in Temporal Bone 7 the squamous epithelium was seen to send projections underneath the everted epithelium into the subepithelial granulation tissue of the ear drum, although they did not extend onto the middle ear side.

Regardless of the type of perforation, the ear canal/ear drum epidermis showed growth activity on the junctional area. In the ears where the immigration was most pronounced the epidermis was often slightly thickened *near the junction*, whereas the basement membrane, with the present methods of study failed to show any specific correlations in this area. Nor was the ear canal inflammation directly correlated with the immigration, although findings suggested subsidence of ear canal inflammation in cases where immigration was most pronounced. On the other hand, mainly subepithelial inflammatory cell infiltration in the middle ear was *present* in all cases, except for Temporal Bone 9 in which case the ear was dry The infiltration, however did not seem to be specifically localized *in* the junction areas.

The width of the transitional area of immigrating squamous epithelium varied from an abrupt change (four ears) to various degrees of a stepwise transition A gradual disappearance of epidermal characteristics could often be noted Frequently *there was a parakeratotic intermediary stage* suggestive of a more primitive keratinization type often followed by the pseudoparakeratotic stage *free from keratinization* before the epithelium was transformed into the normal tympanic types

Sliding an intrusion of the squamous epithelium for a distance of 0 1 to 0 2 mm between the columnar epithelium and the basement membrane, or above the columnar epithelium was seen in three ears All cases with sliding were among the ears with abrupt transition i e. the immigrating squamous epithelium pushed aside the tympanic epithelium and intruded itself underneath (or above) it The situation was not distinctly correlated with the other pathoanatomical subepithelial changes

The most remarkable histopathological finding in connection with immigration was the correlation between its extent and the kind of perforation Although immigration *was seen in almost all ears with central* perforation its extent towards the tympanum was only of an average order of 0.5—0 6 mm The more extensive immigration extending to the promontory (three cases) always occurred among the ears with a total perforation of pars tensa In partly marginal perforations of the pars tensa, the width of immigration was between the above two groups In all three ears with promontorial immigration there was a formation of connective tissue bridges to the medial tympanic wall but in these cases there was also *extensive immigration elsewhere* than along the bridges

Although no instance of attic perforation was seen the ear canal epidermis at the anular area of Shrapnell s membrane showed acanthosis in five ears and even a tendency to depth growth in two. These cases correlate well with the five ears described earlier (p 93) in which depth growth was seen at the junction of the immigrating squamous epithelium (four of them belonged to both groups) Furthermore, the two ears with the depth growth at the region of Shrapnell s membrane also coincided with the ears with pronounced immigration (Temporal Bones *11 12) The inflammation of the ear canal,* on the other hand was in no way correlated with these seven ears (cf Eigler 1951)

5.3 4 *Other findings*

5 3 4 1 Eversion of tympanal epithelium

In two ears the tympanic epithelium was seen to evert (emigrate) onto the ear canal side of the perforation edges This phenomenon was particularly marked in Temporal Bone 7 in which ciliated pseudostratified columnar epithelium with goblet cells could be seen extensively on the ear canal side of the drum In places this everted epithelium was also mucously *changed or metaplastic* The eversion in both cases of the present series, was caused of chronic myringitis in *the edges of central perforation*

5.3 4.2 Epidermal implantation

Epidermal implantation was seen in Temporal Bone 11 This solitary islet of squamous epithelium consisting of stratum basale stratum spinosum and even some granular cells, surrounded by tympanic columnar epithelium and 0.2 mm in diameter had superficial cells showing a slight tendency to parakeratotic scaling Almost the only way it could have developed was that a group of cells of the immigrating epidermis had been *implanted there* without epidermal continuity out of the pouch

5 3 4 3 Cholesterol cyst

A cyst containing cholesterol crystals was found in Temporal Bone 12 Such a cyst is

seen in difficult drainage conditions in chronic otitis and can develop into a cholesterol granuloma (Friedmann, 1959).

5.3.4.4 Tympanosclerosis

Tympanosclerosis implies hyalinization and later sclerosing of the collagenous scar tissue in the tympanum and tympanic membrane. It was seen on the ear drum of the only completely dry ear of the material (Temporal Bone 9). Also Temporal Bone 4 showed characteristics slightly suggestive of tympanosclerosis in the posterior parts of the ear drum remnants.

5.4 TYMPANAL SQUAMOUS EPITHELIUM

Stratified squamous epithelium was seen on the tympanal mucosa in 11 ears, and exceptions were made by the two with eversion. The 11 middle ears showed immigrating squamous epithelium and in five or six of them it was located only in the neighbourhood of the perforation. Metaplastic squamous epithelium was present in only three ears, and in two it contained prickles on the promontory surface. In no instance did the metaplastic epithelium show stratum granulosum or keratinization

Squamous epithelium occurred on the promontory in six ears, equally divided between metaplastic and immigrating types. This change coincided with the total pars tensa defects independent metaplasia and immigration were only once, respectively associated with central perforation of the pars tensa In all six ears the perforation was moist (two ears) or purulent (four ears).

On the tympanic side, only the immigrating type showed epithelium with all the characteristics of epidermis (epidermization). In two ears (Temporal Bones 12, 13) of distinct promontorial immigration the squamous epithelium retained its keratinizing epidermal characteristics almost throughout, the promontory included Once (Temporal Bone 12) it was even "aggressively" hyperkeratotic. In four ears (Temporal Bones 9 11—13) of the most extensive immigration (and one of eversion Temporal Bone 7), the epidermis thickened at or immediately before the junction for a distance of a few tenths of a millimetre. In two ears (Temporal Bones 11 13), increased subepithelial inflammatory cell infiltration was seen from the junction onwards.

The etiology of both promontorial and true tympanic, squamous epithelium seemed to be metaplastic just as often as it was immigrating The tendency to keratosis and depth growth, on the other hand, seemed to belong to the immigrating type only The presence of connective tissue bridges also indicated immigration, although in these cases an extensive immigration from elsewhere was also noted at the same time. The type of the perforation of pars tensa was important in that both the immigration and the metaplasia were more extensive where the perforation had been total.

5.5 KERATINIZATION CHOLESTEATOMA (EPIDERMOSIS)

Opinions concerning a metaplastic etiology of keratinizing squamous epithelium in the middle ear are contradictory Friedmann (1959) and Lim & Saunders (19 2) are among those who found no signs of keratinization in metaplastic squamous epithelium, whereas Sadé (1971) was of the opinion that a metaplastic etiology of cholesteatoma is possible. As early as 1890, Haycroft & Carlier had claimed that the tracheal ciliated epithelium could, under the influence of friction, undergo metaplasia into squamous epithelium and even become keratinized. Auerbach (1956) reported that bronchial ciliated epithelium responded to irritation by squamous epithelial metaplasia showing also prickle cells, but the epithelium was not

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the middle ear surfaces and is slightly or normally keratinizing, or one that is hyperkeratotic, "aggressive" and cholesteatoma forming. Only in Temporal Bone 12 did the epidermis show changes suggestive of the latter type, even then with no cholesteatoma as yet. Had the epidermis in this case (with a medical history exceeding 60 years) originally been cholesteatoma forming, it would definitely already have complicated the otitis with a strong cholesteatomatous process. It is therefore probable that some mesenchymal induction mechanism in a later phase has stimulated the epidermis to change into an active type, hyperkeratotic in character. The patho-anatomical drainage conditions in this case did not differ from those of the rest of the material, a factor to corroborate the view that there must be some mesenchymal inductor(s) present in the transformation of epidermis into the cholesteatomatous type. The high rate of the coincidence of a perforation of Shrapnell's membrane and cholesteatoma, on the other hand, seems to indicate the importance of the patho-anatomical, i.e. drainage conditions. However the marked growing tendency of the epidermis at the region of pars flaccida might also indicate that certain mesenchymal induction mechanisms were particularly epitympanally localized and that even here, in addition to the difficult drainage conditions, also epithelo-subepithelial interactions may contribute for the formation of cholesteatoma.

A comparison of enzymology in cholesteatomatous and non-cholesteatomatous epidermis showed that enzyme activity was usually more pronounced in the cholesteatomatous type (T. Palva et al., 1970 a). According to these authors, the most important qualitative differences were observed in acid phosphatase, 5-nucleotidase and non-specific esterases (see also T. Palva et al., 1971). Recent quantitative analyses (T. Palva et al., in press) of alkaline and acid phosphatase activities of cholesteatoma epithelium and postauricular skin showed significantly larger values in the former tissue.

Abramson & Gross (1971) in cases of cholesteatoma, found that the frequency of collagenase activity in tissue culture containing both the epithelium and the mesenchyma was nearly thrice its frequency in cultures containing only the one or the other. Consequently epithelo-mesenchymal interactions increase collagenase activity and hence also further the development of the destructive process of cholesteatoma.

Collagenase activity in non-cholesteatomatous as opposed to cholesteatomatous epithelial mesenchyma in the middle ear has not been studied. Research of this type, and other tissue culture studies concerned with the interrelationships of middle ear mucosa, middle ear epithelium and mesenchyma will, in the future, evidently shed more light on the problems of the behaviour of middle ear epithelium, the mechanisms of induction, and epidermosis.

keratinized Salm (1957) described epidermoid metaplasia in mammary fibroadenoma with formation of keratin cysts. Furthermore, it is known that e.g in leucoplakia of the oral mucous membranes, both keratinization and a granular cell layer are seen on the squamous epithelium which usually is free from the stratum granulosum (Andrews & Domonkos, 1963)

According to McLoughlin (1961 b) each type of mesenchyma has a characteristic influence on the overflying epithelium. The epidermis of the limb-bud of a five-day old chick embryo was keratinized in isolation (McLoughlin 1961 a) and on dermal mesenchyma (McLoughlin 1961 b) On the gizzard mesenchyma, it became mucus secreting and even ciliated On the central myoblastic area of heart mesenchyma the epidermis became endocardial and on the peripheral fibroblastic area it keratinized extensively Moscona (1961) found that, in 19-day old chick embryos, the epidermis on the mesenchyma of the oviduct keratinized when this explant was treated with oestradiole benzoate, the epidermis was transformed into a typical columnar mucus-secreting epithelium When isolated epidermis was treated with oestrogen, no mucous transformation took place, a sign that mesenchyma was required to mediate this effect According to McLoughlin (1961 b) epithelial differentiation is effected by means of the different intercellular materials produced by fibroblasts and more specifically by means of the basement membrane Mesenchymal induction must also be continuous in order to create and maintain the desired differentiation of the epidermis Fell (1964) on the basis of the work by Wessells (1962) and Dodson (1963) assumed that a condition for keratinization and differentiation of the epidermis is the influence of a substrate permitting the specific polarization of the basal cells

According to Lasnitzki (1963) vitamin A deficiency enhanced keratinization and an addition of vitamin A to a culture (embryonic rat oesophagus) changed the epithelial cells into a mucous type with goblet cells Fitton Jackson & Fell (1963) found also mucous metaplasia in skin cultures (scaly metatarsal skin from 12-day chick embryos) treated with vitamin A After the termination of the effect of vitamin A the keratinization qualities were regenerated, and some basal cells, as they moved up into the central epidermal layers, showed both secretory globules and pre-keratinous filaments, i.e. mucin and keratin synthesis in the same cell According to Moscona (1961) the secretory epithelium may also be keratinized as the oxygen pressure increases, and raising the CO_2 pressure to the normal level inhibits this keratogenic metaplasia in chorionic ectoderm of incubated egg

Although a great deal of theoretical and experimental evidence in favour of keratinizing squamous epithelial metaplasia has been accumulated, the present results corroborate the view that metaplastic squamous epithelium in the middle ear hardly ever keratinizes. In the two middle ears in which metaplasia into the stage of stratified squamous epithelium (with prickle cells) was seen the medical history covered a minimum of 40 years and there was no stratum granulosum or keratinization Thus the cholesteatomatous etiology cannot, in the present author's opinion be explained on the metaplastic basis.

The depth growth of immigrating squamous epithelium at the junctions and the hyperactivity of the epidermis at the annular region of the pars flaccida are very well correlated The cases with the latter phenomenon those of the most pronounced immigration, those with the thickening of squamous epithelium at the junction and the "aggressive" hyperkeratosis in one ear are also correlated. In suitable conditions, all this may lead to the development of epidermosis.

It is apparent that tympanic epidermis may be of two types either one that covers

is adequate, together with a subtotal excision of the promontorial mucosa. It is possible that remnants of squamous epithelium can then even be converted to ordinary tympanal epithelium. But when tympanoplasty cuts off the immigration bridges it is also possible that the natural horizontal migration of even minute keratin amounts is inhibited, with the result that an epidermosis develops. In case of cholesteatoma, owing to the high risk of recurrence, the "aggressively" behaving, expansive epidermo-mesenchymal system always requires a total removal. If at the operation no distinct line can be drawn between the immigrating squamous epithelium and the above system, it is advisable always to remove all the epithelium that is suspected of being squamous.

6 CONCLUSIONS

The middle ear epithelium reacts to chronic inflammation by hypertrophy hyperplasia, metaplasia, squamous metaplasia, and secretory proliferation Not only immigration of squamous epithelium but also epidermization and even epidermosis may occur Emigration of tympanic epithelium is also possible in certain conditions From the present study of the epithelium of chronically infected middle ear the following conclusions, based on 13 serially sectioned temporal bones, can be drawn

1 Respiratory type epithelium which often was secretory lined the middle ear cavity remarkably widely exceeding the limits of the maximal extension reported by Sadé (1966 a) It was localized for the most part in the anterior and inferior tympanum with the cilia extending backward in the form a few (one to four) tapering strips.
2 Epithelial metaplasia, of a mild degree at least, occurred regularly in the chronically infected middle ear
3 Stratified squamous epithelium was present on the tympanic mucosa in most cases The promontorial stratified squamous epithelium was as often of metaplastic as of immigrating origin
4 Metaplastic squamous epithelium showed no tendency to keratinization in any of the cases
5 Immigrating squamous epithelium largely retained its epidermal characteristics and slight keratinizing properties In only one case was it transformed into aggressive looking hyperkeratotic epithelium with a prominent stratum granulosum
6 It is apparent that there must be some mesenchymal induction system which in connection with certain patho-anatomical environmental factors (drainage difficulties, pressure effects on the epithelium attic perforation moisture etc.), makes the squamous epithelium aggressive" hyperkeratotic, cholesteatoma forming The present results corroborate the findings by T Palva et al (1968) and Sadé (1971) that there are various types of squamous epithelium in the middle ear
7 When an operation is performed for chronic otitis media, even if nothing suggestive of cholesteatoma can be seen intraoperatively either by the naked eye or with an operating microscope, there is almost always some amount of squamous epithelium on the tympanic side of the perforation edges or in the tympanum. (Cholesteatoma cholesteatomatous membrane and immigrated epidermis can usually be seen under the operating microscope, though observation of the latter can be somewhat difficult) This finding places added importance to the swing-door plasty recommended by T Palva et al (1969) for both myringo- and tympanoplasties, since it permits a careful inspection of the tympanic side of the drum (edges) and its de-epithelialization and possible de-epidermization

The tympanal squamous epithelium seen is either metaplastic or immigrating It is not necessary to remove the metaplastic, nonkeratinizing squamous epithelium at the operation An immigrating non hyperkeratotic squamous epithelium without an extra induction system, will apparently not change its type In these cases removal of epithelium from the epi and hypotympanum to the perforation edge

that there exist two types of squamous epithelium in the chronically infected middle ear. The serial section method, however, suggests that the non-cholesteatomatous type of squamous epithelium is either immigrating or metaplastic in origin, whereas the cholesteatomatous type is always immigrating. The metaplastic type does not undergo keratinization, and the non-cholesteatomatous immigrating type may retain its properties of slight keratinization permanently and never change into cholesteatomatous, "aggressive" and expansive system of epidermal mesenchyma unless inductors unknown to date are present.

Since the ear drum epidermis regularly grows to the tympanal side of the perforation edges, the swing-door plasty recommended by T. Palva et al. (1969) is advisable in all operations on the chronically infected ear. This technique permits exact operative removal of the tympanic epidermis. In an ordinary non-hyperkeratotic case, a subtotal excision of the mucosa in addition to the marginal de-epithelialization is sufficient. In a case with metaplastic squamous epithelium in the tympanum, it is not necessary to touch the epithelium at all unless this is required because of other tympanic pathology. A cholesteatomatous process can always be seen with the operating microscope (keratotic, light coloured cholesteatomatous membrane) and when this happens, a total removal of the transformed middle ear epithelium is indispensable owing to the risk of recurrence.

In practice, a complete removal of the squamous epithelium if intraoperatively observed in the tympanum is usually the wisest course in operations with closed techniques.

7 SUMMARY

The purpose of the present study was to examine systematically the epithelium of the chronically inflamed middle ear Particular attention was given to the type origin and keratinization characteristics of the squamous epithelium possibly found in the tympanum and to the relationship between the epithelial changes observed and the tympanal pathology in general

Autopsy material comprised 13 chronically infected middle ears, often with a medical history of decades. The temporal bones were serially sectioned after fixation and decalcification. The sections were stained with seven methods Haematoxylin Eosin Alcian Blue PAS Baker Luxol Fast Blue, and modifications by Ladewig and Ayoub-Shklar of the Mallory stain The main method was the H E on which systematical analysis was based.

The middle ear epithelium was found to react to chronic inflammation by hypertrophy hyperplasia, secretory proliferation metaplasia and squamous metaplasia Immigration of squamous epithelium epidermization and even epidermosis were also encountered Emigration of the tympanic epithelium was also possible in certain cases.

As a rule respiratory epithelium which often was secretory lined the tympanic cavity widely in its anterior and inferior parts, extending in some ears to the inner surface of the tympanic membrane to the epitympanum, posterior tympanum and even to the area of the mastoid air cell system The tubo-tympanic ciliated epithelium continued posteriorly in the form of a few (one to four) tapering strips which were mainly localized inferiorly and extended in some ears up to the posterior limits of the middle ear cleft.

Epithelial metaplasia of varying degree was seen in all ears In no case did the metaplastic squamous epithelium, even if stratified show any signs of keratinization.

A certain extent of immigrating squamous epithelium with all its layers except rete pegs was seen in most ears at least in the area of the perforation edge. The junction between the epidermis and the tympanal epithelium varied from a completely abrupt change to a gradual change with a transitional area of varying width Immigration was slightest in cases with central perforation In total perforations of pars tensa the squamous epithelium immigrated extensively into the tympanum reaching over the perforation edges and along connective tissue bridges even to the promontory The promontorial stratified squamous epithelium seen in six cases was as often of metaplastic as of immigrating origin

Immigrating squamous epithelium retained largely the normal characteristics typical of the drum epidermis In one case only was it transformed into an "aggressive" looking hyperkeratotic epidermotic epithelium with a prominent stratum granulosum and showing in some places subepithelial projections.

On the basis of the above findings and bearing in mind that the material contained no distinct cholesteatoma it seemed that not until there is some mesenchymal induction system, in connection with certain pathoanatomical conditions (attic perforation, pressure effects on the epithelium particular inflammatory conditions, etc) does the squamous epithelium become cholesteatomatous.

The present findings support the observations reported by T Palva et al (1968)

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SUPPLEMENT [illegible]

Growth and Spread of Laryngeal and Hypopharyngeal Carcinoma with Reflections on the Effect of Preoperative Irradiation

139 Cases Studied by Whole Organ Serial Sectioning

BY

JAN OLOFSSON, M.D., and
A. W. P. VAN NOSTRAND, M.D.

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JAN OLOFSSON M.D.[1] and
A. W. P. VAN NOSTRAND M.D.[2]

From the Departments of Otolaryngology[1] and Pathology[2]
University of Toronto, Toronto, Canada

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Dr Olofsson is now in the Department of Otolaryngology
Linköping University Linkoping, Sweden

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« En aucune autre partie de l'organisme, on ne trouve rassemblées, en un si petit espace, des formes anatomo-pathologiques si diverses, depuis le simple envahissement des muqueuses et des tissus connectivo-vasculaires lâches sous-muqueux, sous l'aspect exophytique, jusqu'à l'infiltration des divers groupes musculaires laryngiens et jusqu'à la destruction cartilagineuse ou osseuse soit du thyroïd, soit du cricoïde, soit de l'arytenoïd, soit de l'épiglotte, soit même de l'os hyoïde. »

(Coutard, 1937)

"In no other part of the body does one find gathered together in so small space, anatomo-pathological forms so diverse, from the simple invasion of the mucosa and loose vasculo-connective tissues and submucosae, of an exophytic aspect, to the infiltration of the various laryngeal muscular groups, and to the cartilaginous or osseous destruction of the thyroid, or the cricoid, or the arytenoid, or the epiglottic or even of the hyoid."

(Coutard, 1937 translated by Cantril, 1959)

Dr Olofsson is now in the Department of Otolaryngology
Linköping University Linköping, Sweden

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Introduction

INCIDENCE

It is estimated that in the United States of America in the year 1972 650 000 new cases of cancer will be diagnosed (Silverberg & Holleb 1972). The death rate from cancer at all sites is estimated as 345 000. In the same period of time, it is expected that 6 800 new cases of laryngeal carcinoma will be diagnosed, and that 3 050 will die of this disease. Whereas the ratio of male to female is nearly equal in the cancers from all sites, laryngeal cancer is expected to be diagnosed in 6 000 male patients, but in only 800 female patients (males/females = 7.5 : 1). The National Board of Health and Welfare, The Cancer Registry in Sweden (1971) reported 155 564 new carcinomas during the period 1959–1965. The mean population in Sweden during this time was 7.6 million people. 826 new laryngeal carcinomas were reported during this period. The crude annual incidence of laryngeal carcinoma per 100 000 individuals is 2.8 for the males and 0.3 for the females. Laryngeal carcinoma constitutes 1 % of all cancer" among males and 0.1 % among females. The sex ratio (crude) in this Swedish series is 9.3 : 1 (male:female). There is an urban predominance in males which is lacking in females. The incidence of carcinoma of the larynx appears to parallel the rising incidence of bronchial carcinoma (Ackerman & del Regato, 1970). On the other hand, the incidence of hypopharyngeal carcinoma appears to follow more closely the incidence of carcinoma of the oral cavity (Ackerman & del Regato 1970), and does not appear to be rising to the same degree. A male predominance is also seen in the hypopharyngeal tumours with the exception of postcricoid carcinomas which have the reverse sex incidence (Jacobsson, 1951; Ackerman & del Regato 1970; Jørgensen, 1971). 446 new cases of hypopharyngeal carcinoma were reported in Sweden during the period 1959 through 1965 with the ratio of male to female = 1.3 : 1 (crude) (National Board of Health & Welfare. The Cancer Registry 1971).

The vast majority of malignant tumours arising in the larynx and hypopharynx are squamous cell carcinomas, all other types of malignancy arising in this region are rare.

The overall ratio of laryngeal to hypopharyngeal carcinoma varies from country to country (Ackerman & del Regato 1970). (In Toronto approximately 100 new cases of laryngeal carcinoma are seen in a year compared to approximately 30 new cases of hypopharyngeal carcinoma (Bryce, 1972).)

Within the larynx, the major published series report that tumours arising in the glottic region are much more frequent than tumours arising in the supraglottic region (MacComb & Fletcher 1967; Mårtensson et al. 1967; Ackerman & del Regato, 1970; American Joint Committee (AJC), 1971; Ledermann 1971). However in Finland, Lauerma (1967) and Taskinen (1969) report that 67 % of all laryngeal carcinomas arise in the supraglottic region, in Spain Pastor (1969) in a review of 1 056 laryngeal carcinomas reports 60 % and in Italy Pietrantoni & Fior (1958) report that over 50 % arise in the same region. In most series primary subglottic tumours are relatively infrequent (Pietrantoni & Fior 1958; Taskinen, 1969)—usually less than 5 % (Smith et al., 1961; MacComb & Fletcher 1967; Mårtensson et al. 1967; AJC, 1971). Ledermann (1971) reported a figure close to 8 %. Within the hypopharynx, in most series at least 50 to

ryngeal and hypopharyngeal carcinomas in relation to the site of origin of the tumour

Many previous authors (e g Mc'Kenty 1926 St. Clair Thomson & Colledge, 1930· Broyles, 1943 Baclesse, 1949· Ogura, 1955 Tucker 1961 1963 Kirchner 1969· Norris et al 1970) have pointed out different sites of weakness in the laryngeal framework through which the tumours tend to spread. Did our material support their findings?

We studied the specific anatomy in the anterior commissure region and applied this anatomical knowledge in a clinical survey of anterior commissure carcinoma to explain the early invasion of cartilage and spread outside the larynx through the cricothyroid membrane so typical of these tumours

A clinical study to evaluate the effect of preoperative irradiation has been undertaken in Toronto since 1961 (Bryce & Rider 1971) Therefore this clinical study gave us the opportunity to assess histopathologically the effect of irradiation in a series of patients treated with this mode of therapy Similar studies have been published in particular by Goldman and his associates (1961–1972).

Another main task was to use our material for a correlation between clinical and radiological evaluation and assessment, compared with our threedimensional histopathological study (Olofsson et al., 1973). This knowledge, we hoped, should ascertain the accuracy or inaccuracy of our methods of clinical examinations.

An ominous clinical sign in laryngeal carcinoma is the fixation of the vocal cord. The histopathological findings in such cases have been illustrated and a correlation has been made (in these cases) between our clinical assessment and the histopathological findings (Olofsson et al. 1973)

Through these studies we hoped to be equipped with a better understanding of the anatomy and of the growth and spread of laryngeal and hypopharyngeal carcinomas, and of the limitations in our clinical methods of assessment. Thereby we hoped to be able to better assess laryngeal and hypopharyngeal tumours and to select more accurately the patients suited for partial surgery

Neck dissections are not performed in all of our cases, but we thought that we at least should gain some information from those dissections that were performed.

60% of carcinomas arise in the piriform sinus, and the remainder are distributed equally between the postcricoid region and the posterior pharyngeal wall (MacComb & Fletcher 1967 Jørgensen 1971 Bryce 1972) An association between postcricoid carcinoma and Plummer Vinson syndrome has long been recognized (Ahlbom 1936 Jacobsson 1951 Wynder et al. 1957 Jones, 1961 Jørgensen 1971 Richards et al. 1971)

METHODS OF ASSESSMENT

A patient with a laryngeal or hypopharyngeal tumour should first be examined by indirect (mirror) laryngoscopy Following this the larynx and hypopharynx should be radiologically examined. Laryngeal tumours are investigated by soft tissue plain films, laryngeal tomography contrast laryngography and sometimes cinelaryngography Hypopharyngeal tumours and larger laryngeal tumour require also a barium swallow Then direct laryngoscopy (and/or hypopharyngoscopy) should be performed and, preferably the microlaryngoscopy technique described by Kleinsasser (1968) should be used. At the endoscopic procedures biopsy should be done to provide histologic confirmation of the diagnosis. Some surgeons recommend transconioscopy to assess subglottic extension of glottic tumours (Mårtensson et al. 1964 Mårtensson 1967 Sörensen 1970) Despite these various methods of clinical examinations there is still a great discrepancy between the clinical and radiologic findings and the true extent of the tumour growth (Fletcher et al. 1954 Ogura 1955 Tucker 1961 1963 Mårtensson 1967 Olofsson et al 1973)

METHODS OF THERAPY

It is generally accepted that early laryngeal carcinoma, particularly of the glottic region is best treated by primary radiotherapy with preservation of the larynx Surgery is reserved for irradiation failures in this group Some centres prefer laryngofissure and chordectomy for small glottic lesions (Zühlke & Schnepper 1968) The more advanced laryngeal lesions are treated either by primary surgery or by a combination of radiotherapy and surgery (Gisselsson & Lindgren 1952 Jackson et al. 1957 Voutilainen & Touvinen 1962 Bryce et al. 1963 Jackson & Norris, 1963 Silverstone et al 1963 Norris 1964 MacComb 1966 Skolnik, 1966 Holsti & Taskinen 1967 Lauerma 1967 MacComb & Fletcher 1967 Mårtensson et al. 1967 Rygård & Hansen 1967 Dahl et al 1968 Oeser 1968 Perez et al. 1968 Biller et al. 1969 Jørgensen, 1970 Ogura & Biller 1970 Vermund 1970 Bryce & Rider 1971 Jørgensen & Sell, 1971 Lederman, 1971 Morrison 1971 Bryce, 1972, Flynn et al. 1972 Goldman et al 1972)

No unanimity exists with respect to the treatment of hypopharyngeal carcinoma. In some centres at least all hypopharyngeal tumours are treated by primary radiotherapy (Jørgensen 1971 Ennuyer & Bataine 1972) and in others by primary surgery (Harrison 1966–1968) Still others use combined treatment (Biller et al 1969 Ogura & Biller 1970, Bryce, 1971 1972 Lalanne et al 1971 Lord et al 1972 Wang et al. 1972)

Some centres are afraid of giving radiotherapy to younger individuals with laryngeal carcinomas because they are concerned about late radiation changes including radiation induced carcinomas in long term survivors (Hayes et al. 1971)

AIMS OF THIS STUDY

The main purpose of this work was to achieve a better understanding of the growth and spread of laryngeal and hypopharyngeal carcinomas by studying laryngectomy and laryngopharyngectomy specimens by the method of whole-organ serial sectioning. The three-dimensional assessment thus achieved is far superior to the often inadequate sampling of such specimens in most routine laboratories. Our studies were directed to increasing our knowledge of the directional variability of the la

recommended retrograde laryngoscopy through the tracheostoma if tracheotomy had been performed for laryngeal obstruction. It is well established that histopathologically a tumour often has an extension that is much greater than can be assessed clinically (MacKenzie, 1900 McGavran et al., 1959 Norris, 1959 Tucker 1961 1963) Norris & Peale (1966), Goldman et al. (1966), Skolnik et al. (1970) have all demonstrated the difficulties involved in assessing the extension of the tumour especially after previous irradiation. Some oedema most often accompanies radiotherapy of laryngeal carcinoma However in some patients the oedema is more prominent and persists for a long time or recur after the initial oedema has subsided Among these cases we can expect a high percentage of residual or recurrent carcinoma (Calcaterra et al 1972) Another problem in evaluation of postirradiation cases is that the tumour growth is often beneath an intact mucosa. Similar problems have been noted in our own series, and we have stressed particularly the difficulties in assessing the vertical but especially the deep extension of tumours even with the assistance of radiological investigations (Olofsson et al 1973)

WHOLE-ORGAN SERIAL SECTIONING

In most centres the pathological examination of a laryngectomy specimen is poorly performed With little understanding of the anatomic relationships and their application in laryngeal surgery the pathologist samples various obvious area of tumour growth and issues a report Recognizing the great deficiencies and lack of clinical practical value of such examinations, laryngologists have attempted for many years to develop better methods of laboratory assessment Leroux Robert (1936) was *the first* to use a method of whole-organ serial sectioning Smitman (1945) serially sectioned paraffin embedded thyrotomy specimens but did not apply the technique to the whole larynx Kernan (1950) embedded whole larynges in celloidin for serial sectioning *The M.D.* Anderson group (Fletcher et al 1954 MacComb & Fletcher 1967) used a paraffin-embedding technique for the same purpose. Szlezak (1966) took whole organ serial slices from the tumour area which then were processed and embedded in paraffin. It was Tucker (1961) however who popularized the celloidin-embedding technique, which has been employed in a number of other laboratories (Goldman et al., 1964–1972 Kirchner 1969 Harrison, 1969 Delahunty & Nassar 1969 Skolnik, 1970). Hyams (1969) at the Armed Forces Institute of Pathology (A.F.I.P.) refined the paraffin embedding technique which we adapted for use in our own laboratory

GROWTH AND SPREAD

The systematic study of the growth and spread of laryngeal and hypopharyngeal carcinoma in the correlation with the anatomical landmarks has only been carried out since the development of whole organ serial sectioning technique (Leroux-Robert, 1936) Most of the studies performed since 1936 have been concerned with laryngeal rather than hypopharyngeal tumours

Coutard & Valat (1927) noticed that supraglottic carcinomas had specific characteristics. These tumours did not extend to the glottic region. They often crossed the anterior midline to occupy both sides The appearance was *most often of the "cauliflower" type*. In his pioneer work in this field Leroux Robert (1936) emphasized that supraglottic tumours never extended towards the subglottic region He also *observed that* carcinomas of the ventricles often invaded the thyroid cartilage Smitman (1945), using the serial sectioning technique confirmed earlier studies, which suggested that carcinoma limited to the true vocal cord tended to grow to the anterior commissure and on to the opposite cord. He also demonstrated the value of the serial sectioning technique in revealing residual tumour at the resection margins of the specimen.

McKenty (1926) and Broyles (1943) sepa

Background Information

TERMINOLOGY

The more detailed study of laryngeal carcinoma was not possible until Garcia in 1854 introduced the indirect or mirror laryngoscopy technique (St. Clair Thomson 1939) In 1876 Isambert recommended that tumours in the subglottic region should be distinguished from other laryngeal tumours. In 1879 Krishaber divided tumour in the region into intrinsic laryngeal tumours and extrinsic laryngeal tumours. He classified tumours arising at the entrance of the larynx and the outer surface of the larynx as extrinsic and considered these to be more malignant This terminology persisted for the next 50 years. In 1930 St Clair Thomson and Colledge suggested four groups. intrinsic, subglottic, extrinsic and mixed Already in 1937 Quick proposed a less conforming terminology He divided the tumours in "cancer of the larynx and "cancer of the hypopharynx He considered however "cancer of the epiglottis as a separate group Walsh (1947) used the term "intrinsic only for those tumours confined to a true vocal cord and not crossing the anterior commissure. He applied the term "endolaryngeal" to other tumours within the larynx except for the subglottic group The fourth group was the extrinsic or extralaryngeal one.

Baclesse (1949) and Lederman (1952) divided laryngeal tumours into supraglottic glottic and subglottic, and separated these from hypopharyngeal tumours U I C C (Union Internationale Contre le Cancer) (1962) and the A J C (American Joint Committee on Cancer Staging and End Results Reporting) (1962) accepted this terminology and further defined these anatomic areas, with minor variations. The supraglottic region includes the posterior (laryngeal) surface of the epiglottis, the ventricular bands and the ventricular cavities (sinuses) The tip of the epiglottis was excluded by the U I C.C. (1962) but this area was accepted as supraglottic by the A J C. (1962) and has also been accepted by the new U I C.C. classification (1972) The glottic region includes the vocal cords and the anterior and posterior commissures. The A J C. makes no mention of the posterior commissure area. The subglottic region extends to the lower border of the cricoid but excludes the under surface of the vocal cords.

Both the U I C.C. (1962) and the A.J C. (1965) divide the hypopharyngeal area into three regions piriform sinus, postcricoid and posterior pharyngeal wall

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Lederman (1970 1971) also suggested dividing the subglottic region into two parts—one mobile and the other fixed. The upper mobile part is related to the conus elasticus and the thyroarytenoid muscles responsible for movement of the glottis, and the lower fixed part is related to the mucosa lining the cricoid ring.

ASSESSMENT DIFFICULTIES

Even though the clinician has many diagnostic tools with which to assess the extent of tumour growth such assessments are frequently inaccurate Mårtensson et al. (1964) and Mårtensson (1967) pointed out the difficulties to assess subglottic extension and recommended transconioscopy as a diagnostic tool Clerf (1940)

recommended retrograde laryngoscopy through the tracheostoma if tracheotomy had been performed for laryngeal obstruction It is well established that histopathologically a tumour often has an extension that is much greater than can be assessed clinically (MacKenzie 1900· McGavran et al 1959· Norris, 1959 Tucker 1961 1963). Norris & Peale (1966) Goldman et al. (1966) Skolnik et al. (1970) have all demonstrated the difficulties involved in assessing the extension of the tumour espe cially after previous irradiation Some oedema most often accompanies radiotherapy of la ryngeal carcinoma. However in some patients the oedema is more prominent and persists for a long time, or recur after the initial oedema has subsided. Among these cases we can ex pect a high percentage of residual or recurrent carcinoma (Calcaterra et al 1972) Another problem in evaluation of postirradiation cases is that the tumour growth is often beneath an intact mucosa Similar problems have been noted in our own series, and we have stressed particularly the difficulties in assessing the vertical but especially the deep extension of tumours even with the assistance of radiological investigations (Olofsson et al., 1973).

WHOLE-ORGAN SERIAL SECTIONING

In most centres the pathological examination of a laryngectomy specimen is poorly performed With little understanding of the anatomic relationships and their application in laryngeal surgery the pathologist samples various obvious areas of tumour growth and issues a report Recognizing the great deficiencies and lack of clinical practical value of such examinations, laryngologists have attempted for many years to develop better methods of laboratory assessment Leroux-Robert (1936) was the first to use a method of whole-organ serial sectioning Sottman (1945) serially sectioned paraffin embedded thyrotomy specimens, but did not apply the technique to the whole larynx. Kernan (1950) embedded whole larynges in celloidin for serial sectioning. The M D Anderson group (Fletcher et al., 1954 MacComb & Fletcher 1967) used a paraffin-embedding technique for the same purpose. Szlęzak (1966) took whole organ serial slices from the tumour area which then were processed and embedded in paraffin. It was Tucker (1961) however who popularized the celloidin-embedding technique which has been employed in a number of other laboratories (Goldman et al., 1964–1972, Kirchner 1969 Harrison, 1969· Delahunty & Nassar 1969 Skolnik, 1970). Hyams (1969) at the Armed Forces Institute of Pathology (A.F I.P) refined the paraffin-embedding technique, which we adapted for use in our own laboratory

GROWTH AND SPREAD

The systematic study of the growth and spread of laryngeal and hypopharyngeal carcinoma in the correlation with the anatomical landmarks has only been carried out since the development of whole organ serial sectioning technique (Leroux Robert, 1936) Most of the studies performed since 1936 have been concerned with laryngeal rather than hypopharyngeal tumours.

Coutard & Valat (1927) noticed that supraglottic carcinomas had specific characteristics. These tumours did not extend to the glottic region. They often crossed the anterior midline to occupy both sides. The appearance was most often of the "cauliflower" type. In his pioneer work in this field Leroux-Robert (1936) emphasized that supraglottic tumours never extended towards the subglottic region. He also observed that carcinomas of the ventricles often invaded the thyroid cartilage Snitman (1945) using the serial sectioning technique, confirmed earlier studies, which suggested that carcinoma limited to the true vocal cord tended to grow to the anterior commissure and on to the opposite cord He also demonstrated the value of the serial sectioning technique in revealing residual tumour at the resection margins of the specimen.

McKenty (1926) and Broyles (1943) sepa

Background Information

TERMINOLOGY

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the high frequency of pre-epiglottic space invasion by epiglottic tumors and the tendency of laryngeal tumours in general to invade the cartilaginous framework in the ossified portions of the cartilage

Harrison (1970) studied 50 hypopharyngeal tumours by whole-organ sectioning. He confirmed Hiroto's (1963) observation that piriform sinus and postericoid tumours commonly spread submucosally for 5 to 10 mm, and suggested that more radical resection would have controlled the primary disease in some of his patients.

Norris et al. (1970) studied 100 patients with laryngeal carcinoma treated surgically and correlated the findings with the results of a 5-year-follow-up These authors appreciated that the prognosis is much more predictable if one knows the depth of the penetration of the tumour as assessed histopathologically They stressed the need for a threedimensional concept in developing better methods of clinical and radiological evaluation.

Harrison (1971) emphasized that subglottic tumours produce ague symptoms initially and that they often are first recognized when they are extensive and produce dyspnoea, stridor or hoarseness (through invasion of intrinsic laryngeal muscles) He stressed the high frequency of paratracheal nodal involvement, and the clinically undetectable spread of these tumours to the trachea, hypopharynx and thyroid gland. He advocated wide-field excision for such tumours

Kirchner & Som (1971) studied 30 supraglottic tumours and indicated that exophytic lesions tend to remain above the laryngeal ventricle, and the anterior commissure, and that these tumours do not invade the thyroid ala Conversely ulcerative lesions may extend downward across the anterior commissure or anterior part of the ventricle and, in this case, frequently invade and destroy the anterior portion of the laryngeal framework. Of significance to the operating surgeon, microscopically these tumours did not invade the thyroid cartilage unless the inferior edge of the growth was visible below the level of the anterior commissure.

Nassar & Bridger (1971) and Bridger & Nassar (1971 1972) have suggested that the topography of the submucosal glands can influence spread of laryngeal carcinoma.

PREOPERATIVE RADIOTHERAPY

The aim of preoperative radiotherapy is to reduce local recurrence and to decrease the rate of metastasis, without delaying the operative procedures or slowing/preventing healing following surgery However preoperative irradiation delays definitive surgery but this delay is necessary for a proper administration of the radiation and for an optimal effect of the therapy (Powers & Palmer 1968 Moss & Brand, 1969). Earlier it was assumed that preoperative irradiation produces fibrosis and closes the lymphatic channels without changing the filtering function of the lymph nodes (Cady 1965). Animal studies by Engeset (1964) suggested a reduction in filtering capacity beginning two weeks after irradiation and continuing for 6 months.

Preoperative radiotherapy is used in preference to postoperative because after operation, oedema, scarring, and damage to the vascular bed may reduce tumour cell oxygenation, and it is known that poorly oxygenated tumour cells are less sensitive to irradiation (Nias, 1967 Moss & Brand, 1969 Coggle, 1971).

Animal experiments suggest that moderate doses of irradiation have little effect on the primary tumour but do decrease the "take" of transplanted cells (Hoye & Smith, 1961 Feder et al. 1963) and reduce the rate of local recurrence (Inch & McCredie, 1963). Studying tumours in mice Powers and Tolmach (1964) showed that preoperative radiotherapy (500 rads) increased the survival when compared with surgery alone.

Surgery combined with radiotherapy in the treatment of laryngeal and hypopharyngeal carcinomas has been used in many centres.

rately emphasized that early spread of laryngeal tumours tends to occur at the anterior commissure region Ogura (1955) confirmed this finding and further delineated the spread in this region especially noting that once the thyroid cartilage has been invaded spread occurs in all directions within the ossified portions of the cartilage

Baclesse (1949) made major contributions in several anatomic regions of the larynx and emphasized the value of radiologic studies in assessing the growth and spread of laryngeal tumours. He noted that, although tumours of the posterior end of the vocal cords were less common but when they were present they tended to invade the arytenoid and subglottic region earlier in their course and therefore had a bad prognosis. He also noted that supraglottic tumours (except for tumours of the ventricles) do not spread downwards, but that tumours of the glottis and ventricle frequently extended both up and down Thyroid cartilage invasion occurred most frequently in the middle third of the anterior part of the thyroid laminae The proximity between mucosa to cartilage in the depth of the ventricles could be enough to explain this He described the subglottic tumours as flat and irregular with submucosal spread and an ill-defined outline without showing the exuberant proliferation so often seen in supraglottic tumours

Ogura & Bello (1952) advocated prophylactic neck dissection and wide field laryngectomy in patients with fixed cord supra or subglottic involvement or tumours of the piriform sinus. In these cases, metastasis occur more frequently and may be present in impalpable lymph nodes.

In a major study Ogura (1955) studied 59 laryngectomy specimens with combined neck dissections The relationship between the invaded structures and nodal metastasis was tabulated. There was higher incidence of nodal metastasis in the extrinsic group—tumours arising from the base of the epiglottis, aryepiglottic folds, arytenoids and piriform sinuses than in the endolaryngeal tumours—those arising from the vocal cords, ventricles and false vocal cords. He noted a higher incidence of nodal metastasis if the endolaryngeal tumours invaded either the thyroid cartilage or the pre-epiglottic space regardless of the site of origin of the tumour

McGavran et al (1961) also related cervical nodal metastasis to certain characteristics of the primary tumour It was their impression that primary subglottic tumours were rare and that many so classified by other authors were in fact glottic tumour with subglottic extension There was a positive correlation between the frequency of nodal metastasis and poor differentiation of the tumour and nerve sheath invasion but not between nodal metastasis and vascular invasion. Tumours with "pushing margins tended to occur more frequently in the supraglottic region. Tumours with pushing margins had a lower frequency of nodal metastasis than tumours that were more infiltrating. The rate of nodal metastasis was highest in those tumours with a "transglottic distribution (crossing the ventricle occupying both the glottic and supraglottic regions) the rate was next highest in the supraglottic tumours, followed by the subglottic tumours.

Willis (1967) stated that glottic carcinomas first extend horizontally and then vertically He also indicated that the laryngeal cartilages act as physical barriers to tumour spread, and that the tumours usually penetrate the framework through the cricothyroid membrane

Bocca et al (1968) reported that in a study of 160 larynges totally removed for supraglottic tumours they had never observed that even very advanced lesions invaded the floor of the ventricle or the vocal cords

Kirchner (1969) in a review of 76 laryngeal tumours and 24 hypopharyngeal tumours, studied by whole-organ sectioning reviewed the causes of vocal-cord fixation He noted that "transglottic tumours frequently invade the cricothyroid space and that supraglottic tumours tend to be less invasive but that piriform-sinus lesions frequently invade the thyroid ala He drew attention to two other features

Material and Methods

GENERAL

Whole-organ serial sectioning provides a unique method for studying the growth pattern and method of spread of laryngeal and hypopharyngeal carcinomas. By using this method of study we hoped to enhance our knowledge of these lesions, and thereby improve their clinical management.

In Toronto most laryngeal and hypopharyngeal carcinomas are treated by primary radiotherapy. The smaller lesions (T1 and T2) receive radiotherapy alone and surgery is employed for irradiation failure. The larger tumours (T3 and T4) in our series received preoperative radiotherapy followed by surgery either immediately or six weeks later. Primary surgery was reserved for a few small tumours managed by partial laryngectomy for verrucous carcinomas, and for some large bulky tumours which produced airway obstruction. About 100 new laryngeal and 30 new hypopharyngeal carcinomas are seen every year in Toronto.

Since the latter part of 1966, when we began collecting laryngectomy and laryngopharyngectomy specimens from patients with laryngeal and hypopharyngeal carcinoma for whole organ serial sectioning, we have collected 153 specimens from 149 patients. Of these, 139 had squamous-cell carcinoma. Of this total only 3 were obtained at autopsy the remainder were operative specimens. Two specimens were acquired from each of 4 patients, who first underwent partial laryngectomy and subsequently had a total laryngectomy. This report will describe the findings in 139 squamous-cell carcinomas of the larynx and hypopharynx.

The remaining 10 tumours of the series were made up of 4 squamous-cell carcinomas of the upper esophagus, and 1 of the oro-pharynx. There was 1 adenoid cystic carcinoma arising from the subglottic region, 1 adenocarcinoma of the thyroid gland and 2 hypopharyngeal fibrosarcomas. These last two tumours were reported separately (Bradshaw & van Nostrand, 1971). One anaplastic small-cell carcinoma of the larynx was studied and has also been separately reported (Olofsson & van Nostrand, 1972). Most patients in this series have been assessed and the treatment planned in a combined radiotherapy – otolaryngology clinic. After this, radiological examinations have been performed. In all treatment groups (including the preoperative radiotherapy group) reassessment of the tumour extension has always been done before surgery.

Laboratory technique

All specimens in the laboratory were opened, usually dorsally photographed and carefully described. A drawing was then made of each specimen.

Before 1970 the laryngectomy specimens were processed using the celloidin embedding technique described by Tucker (1961). The sections thus obtained were found to be too thick (approximately 25 μ) for an autoradiographic study being done concurrently on the same specimens (Briant et al., 1971). Accordingly we have used a paraffinembedding, subserial, sectioning technique on all specimens since late 1969. This technique which differs little from the standard paraffin sectioning method used in most routine anatomic pathology laboratories, is a modification of the method used in the Otolaryngological Laboratory at the Armed Forces Institute of Patho-

The radiotherapy can be administered post operatively (Leroux Robert 1956 Pietrantoni & Fior 1958 MacComb & Fletcher 1967 Fletcher et al. 1970) Pre and postoperative administration of the radiotherapy the so-called "sandwich method, has also been used (Leroux Robert 1956 see also Goldman et al 1964) Preoperative irradiation is, however the most common method (Goldman & Silverstone 1960 1961 Silverstone et al. 1963 Bryce, 1964 Goldman et al 1964–1972 McGavran et al. 1964 Powers & Ogura, 1965 Skolnik et al. 1966 1968, 1970 Goldman 1967 Biller et al. 1969 Ogura & Biller 1970 Bryce & Rider 1971 Levitt et al. 1971 Roswit et al 1972)

Many centres have used full dose (5 000–7 000 rads) preoperative irradiation. Goldman and his group in New York improved their results by giving elective preoperative irradiation in advanced cancer of the larynx and hypopharynx (Goldman & Silverstone 1960 1961 Silverstone et al 1963 Goldman et al 1964–1972 Goldman 1967 Goldman & Fried man 1969) This group uses 5 500–6 000 rads Cobalt 60 over 5–6 weeks, followed by radical surgery 3–6 weeks after completion of the radiotherapy Constable et al. 1972 also re port improved results with this mode of therapy

On the other hand, Bryce & Rider of Toronto (1971) using an identical mode of therapy for advanced laryngeal carcinoma found no improvement in the 3 year survival rate when they compared this therapy with primary surgery and surgery for irradiation failure control group These authors concluded ever that irradiation therapy could be to divide patients with advanced laryn cancer into those who required early and cal excision for control of their disease those for whom excision of the primary le will probably not be needed Wang et (1972) gave 4 500 rads to advanced supragl and piriform sinus lesions with borderline ability If the tumour showed satisfactory gression after this dose the radiation ther was continued to curative dose and sur was reserved for radiation failure. Howeve the tumour did not respond well the comb radiation—surgery plan was followed

A number of other centres have used m smaller doses of preoperative irradia (1 500–3 000 rads) given 1–4 weeks prior surgery Hendrickson & Liebner (1968) fo no difference when they compared the res in treating advanced supraglottic carcino by 2 000 rads or 5 000 rads preoperatively noticed an improvement in comparison w earlier primary surgery Most other cen using the smaller dose of irradiation 1–4 we prior to surgery have produced inconclus results regarding improved prognosis (McG ran et al. 1964 Powers & Ogura, 1965 H son & Cavanaugh 1965 Roswit et al 19 Biller et al. (1969) and Ogura & Biller (19 noticed a decrease in local recurrence of b of tongue and piriform sinus carcinoma w a low dose of preoperative irradiation.

Fig. 1. Punch card used to record various histopathologic findings on each case. Ruled central portion is used for recording clinical data.

logy (Hyams, 1969) and is very similar to the technique used by the M D Anderson Hospital Laboratory for the same purpose (MacComb & Fletcher 1967) The main difficulties with this technique lie in the increased technical skill needed to section bone cartilage and soft tissues in a block of material the size of the human larynx Much credit for the development of the technique must go to the highly skilled technologists in our own laboratory whose dedicated work contributed much to the development of this method A superior celloidin paraffin double-embedding technique has recently been developed (Ekem 1972)

The bulk of the laryngeal tumours were sectioned in a coronal plane, because this provides more histopathologic information and correlates well with the preoperative radiographic studies (Olofsson et al. 1973) Epiglottic tumours were mainly sectioned in a sagittal plane For hypopharyngeal tumours horizontal sectioning gives more information

The histopathologic features of our cases have been tabulated on a punch card sortable by needle (Fig. 1) The use of this card has allowed easy access to readily correlatable features. The pertinent clinical data is typed into the central lined area.

Incidence

Of the 139 squamous-cell carcinomas in this series, 110 were primary laryngeal tumours, and 29 were primary hypopharyngeal tumours.

Sex (Diagram I II)

Only 7 of the 110 laryngeal tumours occurred in females a ratio of approximately 15 1 male over female Of the 29 hypopharyngeal carcinomas, only 8 occurred in females. Of the 19 patients with piriform sinus tumours only 2 were females, whereas 4 of the 7 postcricoid tumours and 2 of the 3 multiregional tumours occurred in women

Comments The 15 1 male – female ratio in our series of laryngeal tumours is higher than in many other reported series (Wynder et al. 1956 Ackerman & del Regato 1970 National Board of Health and Welfare The Cancer Registry in Sweden 1971) All of our patients had advanced or recurrent carcinoma and all underwent surgery Thus our series is highly selected. With respect to the hypopharyngeal tumours, the ratio of male over female is 2.6 1 A male predominance is in keeping with other reported series (Ackerman & del Regato 1970 Jørgensen 1971) However Jacobsson (1951) in a series of 322 patients had 203 women and The National Board of Health and welfare The Cancer Registry in Sweden (1971) reports a ratio of male over female 1 3 1 (crude) in a review of 446 hypopharyngeal carcinomas. The higher frequency of females in the postcricoid group which has been reported by others may be related to the Plummer Vinson (or Paterson–Brown-Kelly) syndrome (Ahlbom 1936 Jacobsson 1951 Wynder et al 1957 Jones, 1961 Ackerman & del Regato 1970 Richards et al. 1971) although this diagnosis was never established in any of the patients in our series

Age (Diagram I II)

At the time of diagnosis the ages of the 110 patients with laryngeal tumours varied from 37 to 83 years with a mean of 59 years for the men and 63 for the women. As diagram I shows the peak incidence was between 50 and 69 years (71 %) Twenty-one patients were 70 years or older and only 18 were under 50 The tumours in women appear to be fairly evenly distributed through the span 57–83 years.

Patients with hypopharyngeal tumours ranged in age from 42 years to 75 years, with a mean of 59 years for the men and 60 years for the women As with laryngeal tumours, the peak incidence in patients with hypopharyngeal tumours lies between 50–69 years.

Comment The age distribution in this series agrees with that described by other authors both for laryngeal tumours (Pietrantoni & Flor 1958 McGavran et al 1961 Lauerma 1967

complications after a laryngopharyngectomy There was no residual or metastatic tumour at autopsy The smoking habits of this patient are unknown.

The other patient developed a multiregional carcinoma, probably of piriform-sinus origin, 54 years after radiotherapy for thyroid disease This patient was a non-smoker

Comment Irradiation-induced tumours are well recognized and both epithelial tumours, e.g. basal-cell carcinoma, squamous-cell carcinoma and thyroid carcinoma, and mesenchymal tumours. e.g. osteogenic sarcoma, chondrosarcoma, fibrosarcoma and leukemias have been described (Ackerman & del Regato 1970).

Squamous-cell carcinomas of the larynx and hypopharynx have been described following irradiation for pre-existing benign or malignant processes (Goolden 1951 1957 Holinger & Rabbett, 1953 Som & Peimer 1955 Baker & Weissman 1971 Cronin, 1971 Stell, 1971 Schindel & Castoriano 1972) The latent period between the irradiation and the diagnosis of carcinomas was usually 20 to 35 years.

LARYNGEAL CARCINOMA (110 CASES)

Histologic grading

Using Broders classification (Broders, 1932) all the tumours were graded in terms of degree of differentiation (Table I). In all cases, to avoid the changes produced by irradiation therapy the grading was performed on the original biopsy Nine tumours were classified as Grade I and of these 4 were verrucous carcinomas These 4 have been separately reported (van Nostrand & Olofsson, 1972). Of these 9 tumours, 6 were glottic and 3 were supraglottic.

The vast majority of the tumours, 87 were classed as Grade II Sixty of these were glottic, 18 were supraglottic, 3 were subglottic and 6 were of the very large tumours, classified as multiregional.

Twelve tumours were classed as Grade III

Table I *Histologic grading of laryngeal carcinomas (Broders')*

	I	II	III	IV	Total
Supraglottic	3 (1)[a]	18	3	1	25
Glottic	6 (3)[a]	60	7		73
Subglottic		3		1	4
Multiregional		6	2		8
Total	9	87	12	2	110

[a] Verrucous carcinoma.

and of these 7 were glottic, 3 were supraglottic, and 2 were multiregional.

Grade IV tumours were very uncommon we encountered only 2 One of these was supraglottic and the other subglottic.

Comment Most of the tumours in this study were moderately well differentiated lesions. If one excluded the verrucous group, only 7 tumours (5 Grade I and 2 Grade IV) lie at the extremes of differentiation. While Jackson & Jackson (1939 1945) indicated that a biopsy specimen may not necessarily reflect the differentiation of the whole tumor McGavran et al. (1961) found little difference between the biopsies and the excised tumours in a large series of cases A greater proportion of the supraglottic tumours were in the poorly differentiated range. This finding may partially explain the worse prognosis of these tumours.

Table II *Site of origin and anatomic distribution. Carcinoma of the larynx*

Glottic (73)	
Confined to glottic region	13
Subglottic extension	24
Supraglottic extension	5
Sub- and supraglottic extension	31
Supraglottic (25)	
Confined to supraglottic region	11
Glottic extension	5
Oropharyngeal extension	5
Hypopharyngeal extension	3
Glottic, oro- and hypopharyngeal extension	1
Subglottic (4)	
Glottic extension	4
Multiregional (8)	

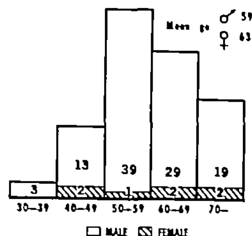


Diagram 1

Taskinen 1969 The National Board of Health and Welfare, The Cancer Registry in Sweden 1971) and for hypopharyngeal tumours (Jacobsson 1951 Pietrantoni & Flor 1958 The National Board of Health and Welfare The Cancer Registry in Sweden 1971).

Etiologic factors

Smoking and alcohol

Cigarette smoking is a significant factor in the causation of laryngeal cancer in men (Wynder et al. 1956 Stell 1971 1972) We have information regarding the smoking habits of 92 of the 110 patients with laryngeal carcinoma. Only 5 were nonsmokers. One patient smoked cigars and 7 smoked pipes. The remaining 79 smoked cigarettes, and 65 of these smoked in excess of 20 cigarettes daily usually for many decades. The smoking habits of 5 of the 7 women were known All 5 were cigarette smokers, and 4 smoked in excess of 20 cigarettes daily

Smoking habits are known in 23 out of the 29 patients with hypopharyngeal carcinoma Nineteen were smokers—17 smoked cigarettes, 1 smoked a pipe and 1 smoked cigars Eleven of the cigarette smokers smoked in excess of 20 cigarettes daily Of the 4 non smokers, 3 were female and 1 was male

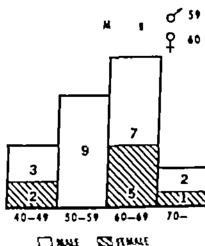
Excessive consumption of alcohol was noted in both laryngeal and hypopharyngeal tumours, particularly in the heavy smoking group.

Comment The association of both excess smoking and alcohol intake with laryngeal and hypopharyngeal carcinomas has been well documented previously (Jacobsson 1951 Wynder et al 1956 1957 Dunn & Dykstra, 1967 MacComb & Fletcher 1967 Surala & Surak 1967 Ackerman & del Regato 1970 Stell, 1971 1972)

Ryan et al (1955) Zechner (1968) and Auerbach et al (1970) demonstrated positive correlation between laryngeal mucosal changes and duration and amount of cigarette smoking habits. Poor oral hygiene and low social standard are other factors of importance but have not been especially reviewed in our series.

Irradiation

Two of the patients with hypopharyngeal carcinomas had previous irradiation to the neck area One of these a woman (Table XV) developed a piriform sinus carcinoma 30 years after radiotherapy for thyrotoxicosis. This tumour was successfully treated by radiotherapy Nine years later at the age of 76 she developed a postericoid carcinoma and died of surgical



Diagram

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Glottic	6 (3)[a]	60	7		73
Subglottic		3		1	4
Multiregional		6	2		8
Total	9	87	12	2	110

[a] Verrucous carcinoma.

Comment Most of the tumours in this study were moderately well differentiated lesions. If one excluded the verrucous group, only 7 tumours (5 Grade I and 2 Grade IV) lie at the extremes of differentiation. While Jackson & Jackson (1939 1945) indicated that a biopsy specimen may not necessarily reflect the differentiation of the whole tumor McGavran et al. (1961) found little difference between the biopsies and the excised tumours in a large series of cases. A greater proportion of the supraglottic tumours were in the poorly differentiated range. This finding may partially explain the worse prognosis of these tumours.

Table II *Site of origin and anatomic distribution Carcinoma of the larynx*

Glottic (73)	
Confined to glottic region	13
Subglottic extension	24
Supraglottic extension	5
Sub- and supraglottic extension	31
Supraglottic (25)	
Confined to supraglottic region	11
Glottic extension	5
Oropharyngeal extension	5
Hypopharyngeal extension	3
Glottic, oro- and hypopharyngeal extension	1
Subglottic (4)	
Glottic extension	4
Multiregional (8)	

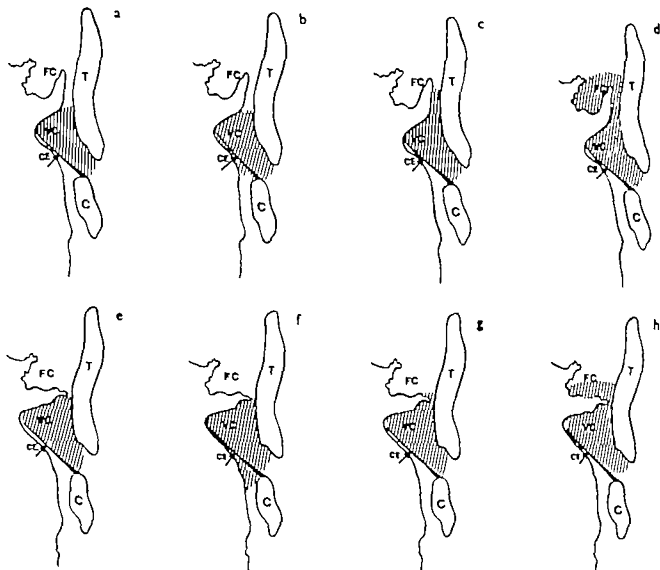


Fig Laryngeal regions as assessed histopathologically Coronal sections of right hemilarynx Sections *a b c d* are all from the anterior portion of larynx (large ventricle) Sections *e f g h* are all from the middle or posterior portion of the larynx. C = cricoid cartilage CE = conus elasticus, FC = false vocal cord T = thyroid ala VC vocal cord

(*a + e*) Maximum extent of a glottic tumour confined to the glottic region
(*b + f*) Glottic tumour with subglottic extension
(*c + g*) Glottic tumour with slight supraglottic extension
(*d + h*) Glottic tumour with marked supraglottic extension.

Site of origin and anatomic distribution (Table II)

In defining the site of origin of the tumours in this series, we have used the basic criteria laid down in the U I C C (1962) system We are well aware of the fact that this classification is based on clinical and radiological examinations and cannot be directly transferred into a histopathological study This present histopathologic study takes the conus elasticus as the structure separating the glottic and the subglottic region in keeping with the boundaries proposed by Lederman (1970 1971) We have considered the lateral angle of the ventricle to be the boundary between the glottic and supraglottic regions (Fig ?) Clinically it has always been difficult to establish the site of origin of laryngeal tumours, but in most cases it is much less difficult to assess the site of origin in serially sectioned operative specimens. However in large tumours which occupy several anatomic regions, classification may still be difficult McGavran et al. (1961) used





Fig. 3. Glottic tumour confined to glottic region. This patient was treated by radiotherapy (5 500 rads Cobalt 60). Partial laryngectomy was performed 14 months later for irradiation failure.

(*a*) Right fronto-lateral partial laryngectomy specimen. The arrow indicates the small localized tumour at the junction of the anterior and middle third of the vocal cord.

(*b*) Coronal section of the specimen taken at the level indicated by the arrow in *a*. The tumour is confined to the free margin of the vocal cord. FC = false vocal cord, T = thyroid ala; VC = vocal cord.

the term "transglottic tumour" to describe a tumour which spread across the laryngeal ventricle to involve both the glottic and supraglottic regions.

Of the 110 cases in this series (see Table II), 73 were primary glottic tumours. Thirteen of these were confined to the glottic region (Figs. 2 *a* and 3), 24 had extended to the subglottic region (Figs. 2 *b* and 4), 5 had extended to the supraglottic region (Figs. 2 *c*, 2 *d* and 27) and 31 had extended to both the supraglottic and subglottic regions (Figs. 2, 7–11, 29). (Sixteen of the tumours in this group would have been classified as "transglottic" by other authors (McGavran et al. 1961, Kirchner 1969).)

Twenty-five tumours arose in the supraglottic region. Eleven of these were confined to the supraglottic region (Figs. 12, 13), but



Fig 4 Glottic tumour with subglottic extension This patient was treated by radiotherapy (1 000 rads Cobalt 60) one day prior to total laryngectomy

( ) Gross photo of the laryngectomy specimen There is a large ulcerated tumour occupying the full length of the right vocal cord with subglottic extension.

(b) Coronal section through the anterior third of the vocal cords. The tumour (as outlined by arrows) occupies the right glottic region and has extended subglottically C = cricoid cartilage FC = false vocal cord T = thyroid ala VC = vocal cord.

two included tip of epiglottis (T4 according to U I C.C 1962) 5 had extended to the glottic region (Figs. 14 15) 5 had extended to the oropharynx 3 had extended to the hypopharynx, and one to glottic region oropharynx and hypopharynx.

Of these 110 tumours 4 arose in the subglottic region and all 4 extended through the conus elasticus to involve the glottic region (Figs. 16 17)

Eight of these tumours were so large that they defied accurate assessment and hence were classed as multiregional (Figs. 18–20) In all probability 6 of these arose in the glottic region All of these tumours would be considered "transglottic" by other authors, thus 24 tumours in the entire series of 110 tumours (22%) would have been so considered.

Comment It has been generally accepted that primary supraglottic tumours tend to have pushing margins and virtually never extend into the glottic regions (Coutard & Valat, 1927 Leroux Robert, 1936 Baclesse 1949 Bocca, 1968 Kirchner & Som 1971)

As a result of this observation horizontal supraglottic partial laryngectomy has been liberally employed in the management of primary supraglottic carcinomas. However in the present series, 6 of the 25 primary supraglottic tumours (24%) had extended below the ventricle into the glottic region (Figs. 14 15)

Szlęzak (1966) made the same observation in his series of serially sectioned specimens. 10 of his 25 supraglottic tumours extended below the ventricle The supraglottic extension of primary glottic tumours, which was much

more common, was observed in 36 of 73 cases (49%) (Figs. 7–11 27 29).

Our number of transglottic tumours 22% (24/110) corresponds well to Kirchner's (1969) figure of 25% (19/76) Many authors suggest that many of these tumours originate in the laryngeal ventricle (Leroux-Robert, 1936 Baclesse, 1949 Kirchner 1969; Ackerman & del Regato 1970)

We believe that tumours originating in the ventricular cavities (sinuses) must be extremely rare. Ogura (1955) classified only 1 of his 43 laryngeal carcinomas as ventricular The laryngeal ventricle is normally lined by ciliated columnar (respiratory) epithelium, and only in a small number of patients who have had radiotherapy to this region have we seen this epithelium change to squamous epithelium. Since squamos carcinoma must arise from squamous epithelium, it seems less likely that such a tumour would arise from the ventricle. Furthermore we have never observed dysplasia of the metaplastic squamous epithelium that is occasionally seen in the ventricle in our post irradiation cases. Finally we have examined a number of autopsy larynges by serial sectioning techniques, and have never observed squamous metaplasia of the ventricular mucosa, not even in those cases with severe dysplasia of the free margin of the vocal cords or false vocal cords.



Fig 5 Spread through the cricothyroid membrane Coronal section through the anterior commissure region of total laryngectomy specimen showing how the tumour (marked by arrows) spreads through the cricothyroid membrane and destroys the lower margins of the thyroid cartilage. This patient had glottic tumour with subglottic extension which was treated by radiotherapy (5 500 rads Cobalt 60) Four and one half months later total laryngectomy and left neck dissection as performed for irradiation failure. C cricoid cartilage; T = thyroid ala.

Clinical management (Table III)

As indicated earlier our patients fell into three broad therapeutic categories: those treated by primary surgery; those having salvage surgery for irradiation failure and those having elective surgery following radiotherapy The 3 patients who came to autopsy are considered separately

Primary surgery

Eighteen patients were treated by primary surgery Of these, 10 had total laryngectomy—5 had primary glottic (Fig. 7), 2 had supraglottic (Figs. 14 15), and 3 had multiregional tumours (Fig. 19). In 5 of these 10 patients, the procedure included a block dissection of the neck (in 1 it was bilateral). Four of these 5 patients had metastatic tumour in cervical lymph nodes. The glottic primary with bilateral



Fig 4 Glottic tumour with subglottic extension This patient was treated by radiotherapy (1 000 rads Cobalt 60) one day prior to total laryngectomy

(*a*) Gross photo of the laryngectomy specimen There is a large ulcerated tumour occupying the full length of the right vocal cord with subglottic extension.

(*b*) Coronal section through the anterior third of the vocal cords. The tumour (as outlined by arrows) occupies the right glottic region and has extended subglottically C = cricoid cartilage FC = false vocal cord T = thyroid ala VC = vocal cord.

two included tip of epiglottis (T4 according to U I C C 1962) 5 had extended to the glottic region (Figs. 14 15) 5 had extended to the oropharynx 3 had extended to the hypopharynx and one to glottic region, oropharynx and hypopharynx.

Of these 110 tumours 4 arose in the subglottic region and all 4 extended through the conus elasticus to involve the glottic region (Figs. 16 17)

Eight of these tumours were so large that they defied accurate assessment and hence were classed as multiregional (Figs. 18–20) In all probability 6 of these arose in the glottic region All of these tumours would be considered transglottic by other authors, thus 24 tumours in the entire series of 110 tumours (22 %) would have been so considered.

Comment It has been generally accepted that primary supraglottic tumours tend to have pushing margins and virtually never extend into the glottic regions (Coutard & Valat 1927 Leroux Robert 1936 Baclesse 1949 Bocca, 1968 Kirchner & Som 1971)

As a result of this observation, horizontal supraglottic partial laryngectomy has been liberally employed in the management of primary supraglottic carcinomas. However in the present series, 6 of the 25 primary supra glottic tumours (24 %) had extended below the ventricle into the glottic region (Figs. 14 15)

Szlęzak (1966) made the same observation in his series of serially sectioned specimens. 10 *of his 25 supraglottic tumours extended below* the ventricle. The supraglottic extension of primary glottic tumours, which was much

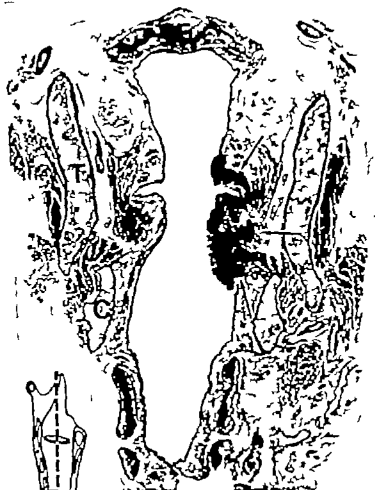


Fig. 7. Glottic tumour with subglottic and slight supraglottic extension. Coronal section through the middle one third of the vocal cords (small diagram indicates the plane of the section). This glottic tumour (as outlined by arrows) has extended subglottically through the conus elasticus, and has also extended around the laryngeal ventricle into the supraglottic region. This patient was treated by primary total laryngectomy. C = cricoid cartilage, E = epiglottis, T = thyroid ala.

Table III. *Clinical management — laryngeal carcinoma (110 patients)*

	Primary surgery		Irradiation failure		Combined therapy 5 500 Rads		Combined therapy 500–2 000 R	Autopsy cases
	Total	Partial	Total	Partial	Total	Partial	Total	
Glottic	5	4	25	8 (2)	23		6	2
Supraglottic	[illegible]	4 (1)[a]	5	2	10[c]	(+1)[c]	1	1
Subglottic			3		1			
Multiregional	3		3				2	
Total	10	8 (1)[a]	36	10 (2)[b]	34	(+1)[c]	9	3
Neck dissection 50 (22)	5 (4)	1 (1)	15 (6)	0	-3 (7)	0	5 (3)	1 (1)

[a] One patient had partial laryngectomy for a verrucous carcinoma of the epiglottis and later had a total laryngectomy because of aspiration. There was no residual tumour in the total laryngectomy specimen.
[b] T patients had partial laryngectomies followed by total laryngectomy for recurrent tumour.
[c] One patient had partial laryngectomy and later had a total laryngectomy because of inability to swallow. There was no residual tumour in the total laryngectomy specimen.

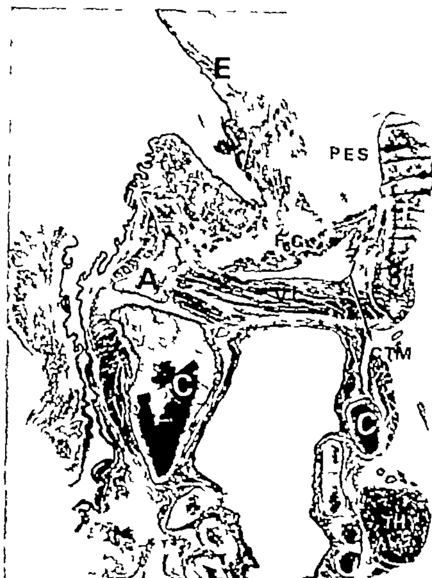


Fig 6 Route of spread through the cricothyroid membrane
Sagittal section of a normal larynx taken close to the midline Tumours involving the anterior commissure region often extend through the cricothyroid membrane (CTM) but in order to do so the tumour must first extend subglottically (Route marked by arrow) A = arytenoid cartilage C = cricoid cartilage E = epiglottis FC = false vocal cord PES = pre-epiglottic space T = thyroid cartilage THY = thyroid gland VC = vocal cord

neck dissections had metastasis to nodes on both sides. Patients with advanced carcinomas, who often had airway obstruction and/or nodal metastasis were treated by primary total laryngectomy

Eight patients were treated by primary partial laryngectomy—4 of these had horizontal supraglottic laryngectomies (Fig 13) 3 had partial vertical laryngectomies and 1 had laryngofissure with cordectomy The 4 horizontal supraglottic laryngectomies were performed for supraglottic tumours 1 of these patients had a combined neck dissection with positive nodes. The remaining 4 tumours were confined to the glottic region and neck dissection was not performed

One patient should be singled out (see Table III) This 77 year-old woman had an extensive verrucous carcinoma of the epiglottis, which was treated by a horizontal supraglottic laryngectomy Four months later a total laryngectomy was performed because she was aspirating saliva and food. We found no residual tumour in the total laryngectomy specimen This case has been separately reported (van Nostrand & Olofsson 1972)

Salvage surgery for irradiation failure

Forty six patients in the series underwent surgery for residual or recurrent tumour after radiotherapy with occasional exceptions they received Cobalt 60 in a dosage of 5 500 rads The interval between radiotherapy and operation varied from 2 months to 87 months (7



Fig 7 Glottic tumour with subglottic and slight supraglottic extension Coronal section through the middle one third of the vocal cords (small diagram indicates the plane of the section) This glottic tumour (as outlined by arrows) has extended subglottically through the conus elasticus, and has also extended around the laryngeal ventricle into the supraglottic region. This patient was treated by primary total laryngectomy C = cricoid cartilage E = epiglottis, T = thyroid ala

Table III *Clinical management — laryngeal carcinoma (110 patients)*

	Primary surgery		Irradiation failure		Combined therapy				Autopsy cases
					5 500 Rads		500–2 000 R		
	Total	Partial	Total	Partial	Total	Partial	Total		
Glottic	5	4	25	8 (2)	23		6		2
Supraglottic	–	4 (1)[a]	5	2	10[b]	(+1)[c]	1		1
Subglottic			3		1				
Multiregional	3		3				2		
Total	10	8 (1)[a]	36	10 (2)	34	(+1)[c]	9		3
Neck dissection 50 (22)	5 (4)	1 (1)	15 (6)	0	23 (7)	0	5 (3)		1 (1)

[a] One patient had a partial laryngectomy for verrucous carcinoma of the epiglottis and later had a total laryngectomy because of aspiration There was no residual tumour in the total laryngectomy specimen
[b] Two patients had partial laryngectomies followed by total laryngectomy for recurrent tumour
[c] One patient had a partial laryngectomy and later had a total laryngectomy because of inability to swallow There was no residual tumour in the total laryngectomy specimen.



Fig 8 Glottic tumour with subglottic and slight supraglottic extension Coronal section through the anterior commissure region of a total laryngectomy specimen The tumour involves mainly the left vocal cord and anterior commissure region and has extended subglottically In other sections from the specimen slight supraglottic extension was also present. Seven years previously this patient had radiotherapy (5 500 rads Cobalt 60) for a tumour of the right vocal cord. Two years later an extended laryngofissure with removal of the anterior portion of the right thyroid ala was performed (arrow denotes absent right ala) Note that the recurrent tumour was mainly at the anterior commissure and on the left side of the specimen C = cricoid cartilage H = hyoid bone T = thyroid ala.

years and 3 months) with the median interval being 18 months.

Thirty-six of these 46 patients were treated by total laryngectomy—25 had primary glottic tumours (Figs. 8 10 11) 5 had primary supra glottic tumours, 3 had subglottic tumours (Figs. 16 17) and 3 had multiregional lesions (Figs. 18 20) Of these 36 15 had combined neck dissection—six had positive lymph nodes (all three of the patients with supraglottic tumours who had neck dissection had positive nodes) One patient with a supraglottic carcinoma had bilateral neck dissection, one of which contained metastatic lymph nodes.

Two patients deserve special mention (Table III) One received radiotherapy for a glottic carcinoma but developed a recurrence two years later which was treated by extended



Fig. 9. *Glottic tumour with prominent subglottic and very high supraglottic extension.* Coronal section through the middle third of the vocal cords, showing tumour occupying both vocal cords with large subglottic extension. The arrows indicate the strikingly sharp superior margin of the tumour. Note also the extensive invasion of the lower one half of both thyroid alae. This tumour also spread outside the laryngeal framework through the cricothyroid membrane and the cricothyroid spaces bilaterally. This patient received 500 rads Cobalt 60 just prior to total laryngectomy. C = cricoid cartilage, E = epiglottis, T = thyroid ala.

laryngofissure. Five years after this operation, a total laryngectomy was performed for a recurrent tumour in the anterior commissure (new) and on the anterior portions of the opposite vocal cord (Fig. 8). The other patient received irradiation for a glottic carcinoma in the region of the vocal process. Six months later a recurrent tumour was treated by a partial vertical laryngectomy. One year later a total laryngectomy was performed for recurrent tumour involving the homolateral hemilarynx.

In 10 other patients, partial laryngectomy was performed for residual or recurrent tumour. None of these had a neck dissection. The primary tumour was glottic in 8 and these were treated by vertical partial laryngectomy (Fig. 3). One patient had a supraglottic

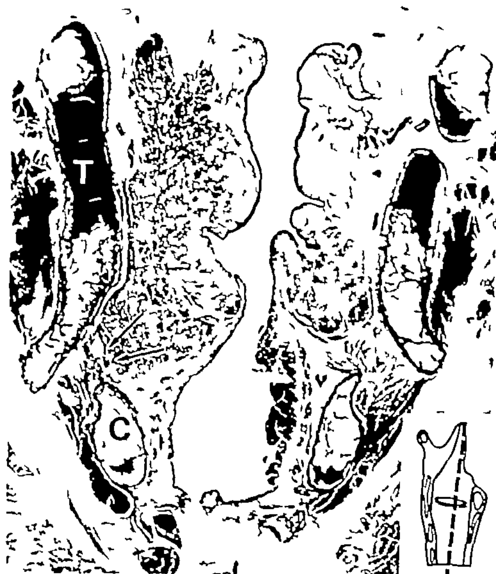


Fig 10 Glottic Tumour with supraglottic and subglottic extension ("transglottic") Coronal section through the middle third of the vocal cords. On the left side the tumour has a transglottic distribution Arrows indicate the tendency for this tumour to spread through the cricothyroid space On the right side the tumour occupies the vocal cord. There is also very marked surface extension of tumour int the subglottic region Thi patient first received radiotherapy (5 500 rads Cobalt 60) for a left glottic tumour with slight subglottic and supraglottic extension. Two years later a total laryngectomy was per formed for recurrent tumour C = cricoid cartilage T = thyroid ala.

primary treated by horizontal supraglottic laryngectomy An additional supraglottic primary tumour had spread to the glottic level and was treated by partial vertical laryngectomy

Combined therapy (elective surgery following radiotherapy)

As a pilot study begun in this centre in 1961 a series of patients with hypopharyngeal and large laryngeal carcinomas were treated by

Fig 11 Extensive tumou beneath i tact mucosa (postirradiation). Three years before laryngectomy th s patient had radiotherapy (5 500 rad Cobalt 60) for a tumour occupying the right ocal cord Because of the development of ocal cord fixation d rect laryngoscopy wa perf rmed One of the four blind biopsies taken contained tumour

(*a*) Gross photograph of the laryngectomy pec men showing sl ght ulceration of mucosa at the anterior commissure and subglotticall on the right ide at the site of the previou b psy

(*b*) Coronal section through the middle third of the ocal cords illustrating large tumour exten ion









beneath mainly intact mucosa. The tumour is ade both supraglottically and subglottically. Note invasion of the thyroid cartilage (T) and cricoid cartilage (C). Arrow indicates tumour outside the thyroid ala. E epiglottis.

( ) Coronal section through the arytenoid region showing extensive tumour lateral to the arytenoid cartilage (A), invasion of the arytenoid and cricoid cartilages, and of the right cricothyroid joint. Note overlying intact mucosa. The arrow indicates tumour spread outside the thyroid ala.

(*d*) Coronal section through the posterior plate of the cricoid cartilage. The tumour invades the right cricoarytenoid joint and adjacent parts of the arytenoid and cricoid cartilages. Note also the invasion of the posterior cricoarytenoid muscle (arrow).



Fig 17 Tumour of the tip of the epiglottis. Five years prior to the present surgery this patient received radiotherapy (5 500 rads Cobalt 60) for a left vocal cord carcinoma. He developed a new primary at the tip of the epiglottis, treated by horizontal supraglottic partial laryngectomy

(*a*) Specimen viewed from the laryngeal surface showing the ulcerated tumour at the tip of the epiglottis.

(*b*) Sagittal section through the specimen at the site of the tumour Note how the tumour surrounds and destroys the upper portion of the epiglottic cartilage. E = epiglottis; H = hyoid bone; T = thyroid cartilage

radiotherapy followed by elective laryngectomy or laryngopharyngectomy Most of these patients received 5 500 rads of Cobalt 60 followed by *surgery six weeks later A much smaller* number of patients received 500–2 000 rads, followed by surgery within 24–48 hours. This clinical study showed that in patients (treated from 1961 to 1966) with advanced laryngeal carcinoma, the combined method of treatment did not conclusively give a better five year survival than salvage surgery for irradiation failure or primary surgery (Bryce & Rider 1971) *However other authors report more* positive results with this mode of therapy (Goldman et al. 1964–1972 Constable et al 1972) From this study we received laryngectomy specimens from 43 patients with laryngeal carcinoma. Thirty four of these spec*imens are from patients who had a full course* of radiotherapy followed by surgery six weeks later Of these 34 23 were primary tumours of the glottic region (Figs. 27 29) 10 were primary tumours of the supraglottic region (Fig 28) and 1 was a primary tumour of the subglottic region All 34 patients in this group *had a total laryngectomy In 33 this was the* primary mode of surgical therapy However one patient (Table III) a 51 year-old man had a horizontal supraglottic laryngectomy after a course of 5 500 rads of Cobalt 60 for an epiglottic carcinoma Eleven months later he had a total laryngectomy because he could not swallow There was no residual or recurrent tumour in the total laryngectomy specimen

The remaining 9 patients in the group had 500–2 000 rads followed by surgery mainly within 24–48 hours later Six had primary glottic tumours (Figs. 4 9) 1 had a primary supraglottic tumour and 2 had multiregional tumours.

Of the 43 patients treated by elective surgery after radiotherapy 28 had a neck dissection Ten of these had positive nodes.



Fig. 13. Epiglottic tumour with invasion of the pre-epiglottic space. Primary horizontal supraglottic partial laryngectomy for an epiglottic-aryepiglottic fold tumour.

(*a*) Sagittal section through the specimen showing how the tumour occupies the posterior (laryngeal) surface of the epiglottis, but penetrates through the dehiscences (fenestrations) in the cartilage and in the lower portion slightly invades the pre-epiglottic space. E = epiglottis, H = hyoid bone.

(*b*) Enlarged view of rectangle outlined in Fig. 13. Note how the tumour penetrates the dehiscences (fenestrations) of the epiglottic cartilage without destruction of the cartilage.

Autopsy cases

Three specimens were obtained at autopsy.

One patient received irradiation for a glottic carcinoma six years before his death. He was lost to follow-up until two years before his death, when he appeared with a huge recurrent bilateral inoperable tumour. He received further radiotherapy but died two years later with massive residual laryngeal tumour and multiple cervical nodal metastasis.

Another patient received radiotherapy one year before he died, for an epiglottic tumour without palpable lymph nodes. Metastatic tumour was present in multiple lymph nodes from a neck dissection performed nine months later. He developed metastasis in the opposite side of the neck and died of his disease three months later. At autopsy there was extensive tumour in the neck but no residual tumour at the primary site.

The third autopsy case had a primary glottic tumour with subglottic extension. Combined therapy was planned for this patient, but during his radiotherapy he developed thrombosis of his right carotid artery and died of cerebral infarction. Acute radiation effect was present in the tumour of his larynx (Fig. 30).

Spread of laryngeal carcinoma

The growth and spread of laryngeal carcinoma is largely determined by the site of origin of the primary tumour. The major factors in determining the direction and extent of tumour growth are the anatomic barriers produced by the laryngeal compartments so well

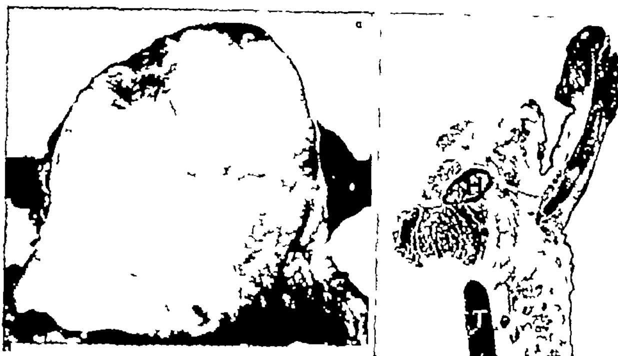


Fig 12 Tumour of the tip of the epiglottis Five years prior to the present surgery this patient received radiotherapy (5 500 rads Cobalt 60) for a left vocal cord carcinoma. He developed a new primary at the tip of the epiglottis treated by horizontal supraglottic partial laryngectomy

(a) Specimen viewed from the laryngeal surface showing the ulcerated tumour at the tip of the epiglottis.

(b) Sagittal section through the specimen at the site of the tumour Note how the tumour surrounds and destroys the upper portion of the epiglottic cartilage E = epiglottis; H = hyoid bone T = thyroid cartilage.

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The remaining 9 patients in the group had 500–2 000 rads followed by surgery mainly within 24–48 hours later Six had primary glottic tumours (Figs. 4 9) 1 had a primary supraglottic tumour and 2 had multiregional tumours.

Of the 43 patients treated by elective surgery after radiotherapy 28 had a neck dissection Ten of these had positive nodes.

Table IV *Glottic carcinoma confined to larynx* (46)

Invasion of cartilage

Cartilage	Carcinoma confined to glottic region (13)	Glottic carcinoma with subglottic extension (17)	Glottic carcinoma with supraglottic extension (5)	Glottic carcinoma with sub- & supraglottic extension (11)	Total (46)
Thyroid	—	—	—	4	4
Cricoid	—	2	—	4	6
Arytenoid	—	6	2		15

in Tables IV–XI. Patterns of spread in each of the laryngeal regions will be discussed separately.

Glottic carcinoma

Most of the tumours which arise in the glottic region originate on the free margins of the vocal cords. In this study the inferior boundaries of the glottic region is the conus elasticus, and the superior boundary is the lateral angle of the laryngeal ventricle (Fig. 2). Following the U I C C system we have included the anterior and posterior commissures in the glottic region.

Of the 73 tumours of glottic origin, 13 were confined to the glottic region (see Table II Figs. 2 and 3), 55 extended into the subglottic region—24 of these spread to the subglottic region alone (Figs. 2 and 4), while the remaining 31 spread to both the subglottic and supraglottic regions (Figs. 2, 7–11, 29). An additional 5 tumours of glottic origin spread to the supraglottic region alone (Figs. 2 and 27), making a total of 36 cases with supraglottic spread.

In 35 of these 73 glottic tumours, spread had occurred to the opposite hemilarynx. In the 13 cases, where the tumour was confined to the glottic region, it crossed the anterior commissure to involve the opposite vocal cord in only one case. Similarly in only 1 of the 5 tumours with supraglottic extension alone did the tumour cross the anterior commissure to the opposite vocal cord. Of the 24 tumours with subglottic extension, 10 had crossed the anterior commissure an 1 had crossed the posterior commissure to involve the opposite vocal cord. Of the 31 cases with subglottic and supraglottic extension, 21 had crossed the anterior midline to the opposite hemilarynx—19 of these were at the anterior commissure (glottic) level, and 2 had crossed anteriorly at the false vocal cord level only. Five tumours had crossed the posterior commissure to the opposite hemilarynx—4 of these had crossed both the anterior and posterior commissures.

Invasion of one or more of the intrinsic laryngeal muscles was common and was observed in 57 out of 73 tumours in this group.

Table V *Glottic carcinoma extending outside larynx* (27)

Invasion of cartilage and spread outside larynx

	Glottic carcinoma with subglottic extension (7)	Glottic carcinoma with sub- and supraglottic extension (20)	Total (27)
Invasion			
Thyroid cartilage	3	19 (17 through)	22
Cricoid cartilage	2	12	14
Arytenoid cartilage	2	14	16
Spread through			
Cricothyroid membrane	7	15	22
Cricothyroid space	—	14	14

3 [illegible]

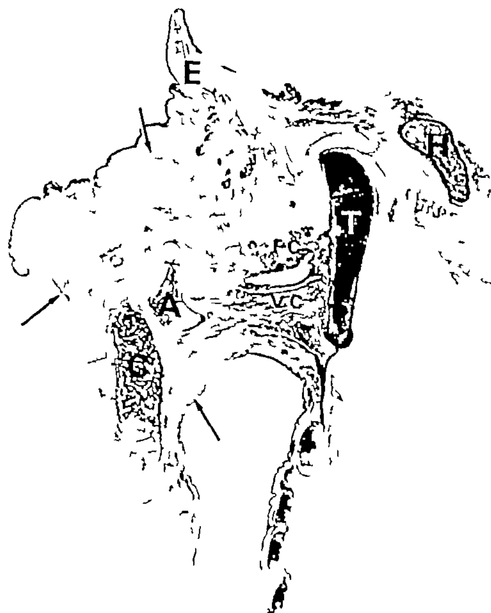


Fig 14 Supraglottic tumour with extension to glottic and subglottic regions Sagittal section to the left of the midline of a total laryngectomy specimen. The tumour (as outlined by arrows) extends posteriorly to the postcricoid region and also extends down in the posterior commissure region to involve the glottic and subglottic regions. This patient had a primary laryngectomy for a large aryepiglottic fold-false vocal cord tumour overlying the left arytenoid cartilage A = arytenoid cartilage C = cricoid cartilage E = epiglottis; FC = false vocal cord H = hyoid bone T thyroid cartilage VC = vocal cord

described by Pressman (1956) Pressman et al. (1960) and Tucker & Smith (1962) Submucosal tumour spread is a feature common to all laryngeal and hypopharyngeal carcinomas. It is the most common method by which laryngeal tumours cross from one side of the larynx to the other and also the route by which tumours cross the laryngeal ventricle Tumours spreading along the length of the vocal cord do so within Reinke s space. As noted earlier the cartilaginous framework of the larynx provides an anatomic barrier to the spread of tumours This framework however has points of weakness which the tumours seek out These points of weakness will be amplified when dealing with tumours arising in a specific region Structures invaded by the laryngeal tumours in our series are detailed

Table IV *Glottic carcinoma confined to larynx (46)*

Invasion of cartilage

Cartilage	Carcinoma confined to glottic region (13)	Glottic carcinoma with subglottic extension (17)	Glottic carcinoma with supraglottic extension (5)	Glottic carcinoma with sub- & supraglottic extension (11)	Total (46)
Thyroid	—	—	—	4	4
Cricoid	—	2	—	4	6
Arytenoid	—	6	2	7	15

in Tables IV–XI. Patterns of spread in each of the laryngeal regions will be discussed separately.

Glottic carcinoma

Most of the tumours which arise in the glottic region originate on the free margins of the vocal cords. In this study, the inferior boundaries of the glottic region is the conus elasticus, and the superior boundary is the lateral angle of the laryngeal ventricle (Fig. 2). Following the U.I.C.C. system, we have included the anterior and posterior commissures in the glottic region.

Of the 73 tumours of glottic origin, 13 were confined to the glottic region (see Table II, Figs. 2 and 3). 55 extended into the subglottic region—24 of these spread to the subglottic region alone (Figs. 2 and 4), while the remaining 31 spread to both the subglottic and supraglottic regions (Figs. 2, 7–11, 29). An additional 5 tumours of glottic origin spread to the supraglottic region alone (Figs. 2 and 27), making a total of 36 cases with supraglottic spread.

In 35 of these 73 glottic tumours, spread had occurred to the opposite hemilarynx. In the 13 cases, where the tumour was confined to the glottic region, it crossed the anterior commissure to involve the opposite vocal cord in only one case. Similarly, in only 1 of the 5 tumours with supraglottic extension alone did the tumour cross the anterior commissure to the opposite vocal cord. Of the 24 tumours with subglottic extension, 10 had crossed the anterior commissure an 1 had crossed the posterior commissure to involve the opposite vocal cord. Of the 31 cases with subglottic and supraglottic extension, 21 had crossed the anterior midline to the opposite hemilarynx—19 of these were at the anterior commissure (glottic) level, and 2 had crossed anteriorly at the false vocal cord level only. Five tumours had crossed the posterior commissure to the opposite hemilarynx—4 of these had crossed both the anterior and posterior commissures.

Invasion of one or more of the intrinsic laryngeal muscles was common and was observed in 57 out of 73 tumours in this group.

Table V *Glottic carcinoma extending outside larynx (27)*

Invasion of cartilage and spread outside larynx

	Glottic carcinoma with subglottic extension (7)	Glottic carcinoma with sub- and supraglottic extension (20)	Total (27)
Invasion			
Thyroid cartilage	3	19 (17 through)	22
Cricoid cartilage	2	12	14
Arytenoid cartilage	2	14	16
Spread through			
Cricothyroid membrane	7	15	22
Cricothyroid space	—	14	14

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Fig 14 Supraglottic tumour with extension to glottic and subglottic regions Sagittal section to the left of the midline of a total laryngectomy specimen The tumour (as outlined by arrows) extends posteriorly to the postcricoid region and also extends down in the posterior commissure region to in ol e the glottic and subglottic regions This patient had a primary laryngectomy for a large aryepiglott c fold-false vocal cord tumour overlying the left arytenoid cartilage A = arytenoid cartilage C cricoid artilage E epiglottis FC = false ocal cord H hyoid bone T thyroid cartilage VC ocal cord

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In addition to these 9 cases with positive cervical nodes, 5 more had metastatic tumour in the prelaryngeal (Delphian) node/s/ (Fig. 21 *a*), making a total of 14 with positive nodes at the time of laryngectomy (Table XII).

Comment. Vertical extension of tumours arising from the glottic region into the subglottic or supraglottic regions occurred more frequently than horizontal extension to the opposite hemilarynx, an observation also made by Pressman et al (1960).

However the conus elasticus resisted tumour invasion for a long time and could in some cases be seen bulging downwards. Meurman (1936) noted that elastic fibers were very resistant to "the pathologic influence of the tumour"

Glottic tumours which spread outside the laryngeal framework do so most commonly through the cricothyroid membrane or cartilage at the anterior commissure (Figs. 5 6, 21 *b*). This would appear to be related to the ease with which these tumours spread along the vocal cord within Reinke s space, and also to the close proximity of the mucosa to the thyroid ala at the anterior commissure with no intervening muscle Ridpath (1930) first described the fibrous cord in the anterior midline that Broyles (1943) called the "anterior commissure tendon" This tendon blends with the underlying cartilage without coverage of perichondrium Glottic tumours, when they reach the anterior commissure, very rapidly extend subglottically to penetrate the cricothyroid membrane and escape outside the laryngeal framework (Fig 6) (Ogura, 1955 Shaw 1965 Willis, 1967 Olofsson et al. 1972). In our series, 22 of the 27 cases with spread outside the larynx used this pathway of exit. Nassar and Bridger (1971) and Bridger and Nassar (1971 1972) have suggested that the submucosal glandular structures in this region make a significant contribution to this method of spread

Glottic tumours that invade the thyroid cartilage tend to do so at the anterior commissure (McKenty 1926 Broyles, 1943 Ogura, 1955)—a feature also explained by the close proximity of the cartilage to the vocal cord with no intervening muscle In our series the thyroid cartilage was invaded in 26 cases, and in 21 of these the invasion occurred at the anterior commissure. In 17 of these the tumour penetrated the thyroid cartilage to extend outside the larynx (Figs. 5 21 *b*). (As would be expected, the larger and more extensive tumours with both supraglottic and subglottic extension included all 17 of these cases.) In addition to invading the thyroid cartilage, many of these tumours also had penetrated the cricothyroid space laterally (Figs. 9 29).

Several other authors have drawn attention to these same features by referring to these large tumours, which traverse the ventricle, as "transglottic" (McGavran et al., 1961 Kirchner 1969). Baclesse (1949) also noted that tumours which surrounded the ventricle invaded the cartilage early and suggested that proximity of the tumours to the thyroid ala could explain this observation. The spread within the paraglottic space is perhaps another important factor (Pressman et al., 1960; Tucker & Smith, 1962)

When invasion of the laryngeal framework occurs, it is the ossified portions of the framework which receive the brunt of the attack (Szlęzak, 1966 Kirchner 1969 Norris et al. 1970) Ogura (1955) also noted that tumour well within the cartilage spread in all directions until the external perichondrium was invaded. Similar findings were present in our series (Figs 5 9 11 29). Occasionally in the very large tumours, we noted islands of residual cartilage surrounded by tumour

Supraglottic carcinoma

The supraglottic region is bounded inferiorly by the vocal cords (Fig. 2), and superiorly by the free margin of the epiglottis and the aryepiglottic folds (following the U.I.C.C. system).

Twenty-five tumours in this series arose in the supraglottic region—15 on the dorsal surface of the epiglottis and the remaining 10 on

As one would expect most of the 16 tumours where no muscle invasion was observed were small superficial lesions confined to the vocal cord The muscle most frequently invaded was the thyroarytenoid (Table XI)

In 46 of the 73 glottic carcinomas, the tumour remained confined to the larynx. Twenty-one of these had invaded one or more of the laryngeal cartilages (Table IV) None of the smaller tumours which were confined to the glottic region invaded cartilage (Fig 3) The arytenoid cartilage was the most frequently invaded (15 cases) The thyroid ala was invaded by 4 tumours and in 3 of these invasion occurred at the anterior commissure region

In 27 cases (the remainder of the total group of 73) the tumour had spread beyond the larynx. The spread outside the laryngeal framework was either through the thyroid ala (Figs. 5 9 29) or through the cricothyroid membrane anteriorly (Figs. 5 6 21 *b*) and/or through the cricothyroid space (spaces) laterally (Figs. 9 10 29) (Table V) In 25 of the 27 the tumour involved one or more of the laryngeal cartilages in only 2 did it penetrate through the cricothyroid membrane without involving the cartilages. The most common site of invasion with penetration and breakthrough of the cartilage was the thyroid cartilage near the anterior commissure (Fig. 5) However in only 2 of the 27 cases with extension outside the larynx was the sole mode of exit through this cartilage In an additional 15 cases, penetration of the thyroid ala was combined with extension through the cricothyroid membrane or space If a glottic carcinoma involves the anterior commissure and extends subglottically it is close to the cricothyroid membrane and escapes by this route early and often (Fig 6) It did so in 22 of our cases. This particular escape route unaccompanied by lateral extension through the cricothyroid space was seen in all 7 of the cases with vertical distribution confined to the glottic and subglottic regions (Fig. 5) In contrast of the 20 larger tumours involving glottic supraglottic and subglottic regions 15 had escaped through the cricothyroid membrane anteriorly but of these 11 had also extended laterally through the cricothyroid space—four of them bilaterally This group of 20 tumours included 9 that other authors (McGavran et al. 1961 Kirchner 1969) would have classed as transglottic tumours (Figs. 10 29)

Several of the very extensive tumours used more than one portal of exit. Four tumours had large subglottic extension and involvement of the upper trachea, as well as lateral spread through the cricothyroid space Four tumours invaded the thyroid gland by direct extension and another had metastasized to the thyroid gland. Two of the tumours had extended into the pre-epiglottic space and both of these involved the base of the epiglottis (Table X)

Vascular invasion was less frequent than we expected and was noted in only 19 cases. McGavran et al. (1961) reported a similar figure No vascular invasion was noted in any of the 13 tumours confined to the glottic region All 19 instances occurred in the 55 glottic tumours with subglottic extension. Most of the invaded vessels were immediately beneath the conus elasticus near its base Eighteen of these 19 cases also had cartilage invasion.

Perineural invasion was observed in 12 cases and was usually noted in the connective tissue deep to the thyroarytenoid muscle near the lower end of the thyroid ala (branches of the recurrent laryngeal nerve) Perineural invasion could sometimes be observed many mm from the main tumour mass. All but three of these cases also had vascular invasion

Of the total 73 cases, 29 had a neck dissection performed at the time of laryngectomy (one patient had bilateral neck dissection—both with metastasis to the lymph nodes) Fourteen of these dissections were performed in the group of 46 cases where the tumour was confined to the larynx—three of these had metastatic carcinoma in cervical nodes. Fifteen of the dissections were performed in the group of 27 cases where the tumour had spread outside the larynx—six had metastatic carcinoma in cervical nodes (Table XII)

In addition to these 9 cases with positive cervical nodes, 5 more had metastatic tumour in the prelaryngeal (Delphian) node/s/ (Fig. 21 *a*), making a total of 14 with positive nodes at the time of laryngectomy (Table XII).

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Supraglottic carcinoma

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Twenty-five tumours in this series arose in the supraglottic region—15 on the dorsal surface of the epiglottis and the remaining 10 on



Fig 15 Supraglottic tumour with extension to the glottic region. This patient had a huge supraglottic tumour treated by primary laryngectomy and right neck dissection. Metastatic carcinoma was present in the cervical lymph nodes, and was also present in the left neck dissection subsequently performed

(*a*) Gross photograph of the laryngectomy specimen viewed from the posterior aspect with the cricoid opened in the midline. There is a large fungating tumour mass occupying the base of the epiglottis, the *right aryepiglottic fold the right false vocal cord* and overhanging the vocal cords.

Fig 15 continued

(*b*) Coronal section of the laryngectomy specimen taken close to the anterior commissure. Note the large tumour invading the pre-epiglottic space

(*c*) Coronal section through the middle third of the vocal cords showing the large tumour mass occupying *the pre-epiglottic space and the right false vocal cord.*

(*d*) Coronal section through the vocal process region showing the tumour at the base of the epiglottis, in the pre-epiglottic space the right aryepiglottic fold and the right false vocal cord with extension down into the glottic region (below the inner angle of the ventricle). Note the pushing margins.

(*e*) Coronal section through the arytenoid region *illustrating how the tumour extends deep to the right* arytenoid cartilage. Note also the partial destruction of the epiglottic cartilage. A = arytenoid cartilage C = cricoid cartilage E = epiglottis H = hyoid bone T = thyroid ala.

the false vocal cords, the laryngeal side of the aryepiglottic folds and arytenoid regions. We were unable to identify any tumours which were confined to the false vocal cords

In 11 cases, the tumour was confined to the supraglottic region (Figs. 12 13) 6 had spread to the glottic region (Figs 14 15) 6 to the vallecula and 4 to the piriform sinus. These totals included one very large tumour that had spread to the glottic region the vallecula and piriform sinus. (Table II)

The opposite hemilarynx was involved in 9 of the 25 cases—seven at the anterior midline and 2 at the posterior midline One of those that crossed the posterior midline arose from the mucosa overlying the arytenoid and ex



tended inferiorly through the posterior commissure region (Fig. 14).

Of the six tumours with glottic extension, only 2 invaded intrinsic muscles and only one impaired the mobility of the vocal cord (see Table XI).

Invasion of the laryngeal cartilages occurred infrequently except for the epiglottic cartilage



Fig 15 Supraglottic tumour with extension to the glottic region This patient had a huge supraglottic tumour treated by primary laryngectomy and right neck dissection Metastatic carcinoma was present in the cervical lymph nodes, and was also present in the left neck dissection subsequently performed.

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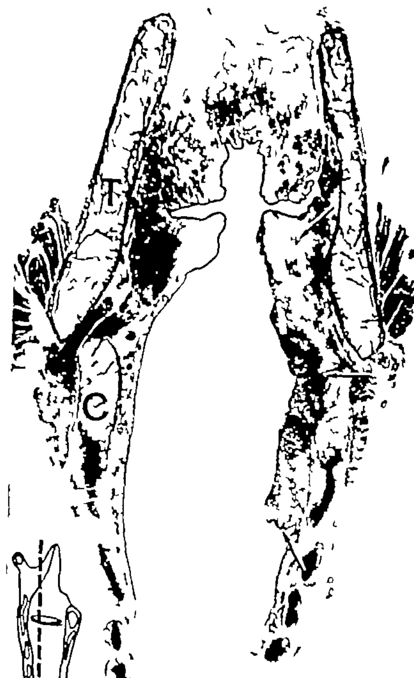


Fig 16 Subglottic tumour Coronal section of a total laryngectomy specimen at the level of the anterior third of the vocal cords. The subglottic tumour (as outlined by arrows) extends up into the glottic region through the conus elasticus, and down to the lower margin of the cricoid cartilage. This patient had a total laryngectomy and a right neck dissection (containing metastatic carcinoma) 3½ months following a full course of radiotherapy (5 500 rads Cobalt 60). C = cricoid cartilage T = thyroid cartilage

(see Table VI) This cartilage was invaded by 10 of the 15 primary epiglottic tumours (Figs. 12, 15) and by another tumour arising in the aryepiglottic fold Two tumours originating on the dorsal surface of the epiglottis penetrated the thyroid cartilage high in the mid line anteriorly and extended outside the larynx. Both had also extended into the preepiglottic space (PES) A total number of ten of the primary epiglottic tumours invaded the preepiglottic space (PES) (Table VII)

Table VI *Supraglottic carcinoma (25)*
Invasion of cartilage

Thyroid	2
Cricoid	1
Arytenoid	4
Epiglottic	11

In the whole group of 25 cases with supra glottic tumours, 14 had neck dissection in combination with the laryngectomy procedure —in 9 the tumour had already spread to the neck nodes one had a bilateral neck dissec



Fig. 17. Subglottic circumferential tumour. Coronal section through a total laryngectomy specimen close to the anterior commissure. The tumour (as outlined by arrow) does not involve the free margins of the vocal cords, but penetrates the conus elasticus into the left vocal cord. This primary subglottic tumour had circumferential distribution within the subglottic region. This patient had a total laryngectomy 5½ months following full course of radiotherapy (5 500 rads Cobalt 60). C = cricoid cartilage; E = epiglottis, T = thyroid ala.

tion—one side contained positive nodes (Table XII).

Vascular invasion was noted in only one of our supraglottic cases and perineural invasion of the superior laryngeal nerve was noted in 3 cases.

Comment. Supraglottic tumours which spread beyond the supraglottic region tend to spread either upwards and outwards, or downwards—seldom in both directions. These tumours tend to have "pushing" margins (Fig. 15). As indicated earlier in this study, nearly one quarter of the supraglottic tumours extended into the glottic region (Figs. 14, 15), contrary to the experience of other authors.

Coutard & Valat (1927), Leroux Robert (1936) and Baclesse (1949) and later Bocca et al. (1968) noted that supraglottic tumours do

Table VII. *Epiglottic carcinoma (15 out of the 25 patients with supraglottic carcinoma)*

Invaded structure	
Epiglottic cartilage	10
Thyroid cartilage	2
Pre-epiglottic space	10

Table VIII. *Subglottic carcinoma (4)*

Invasion of cartilage	
Thyroid	2
Cricoid	2
Arytenoid	1

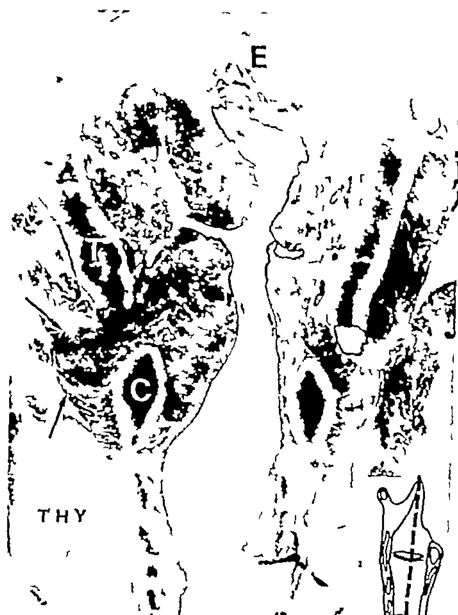


Fig 18 Multiregional tumour with transglottic distribution Coronal section of a total laryngectomy specimen through the middle third of the vocal cords There is a large tumour with a "transglottic distribution" occupying the left side of the larynx with subglottic extension The arrows indicate the spread outside the larynx through the cricothyroid space The lower border of the thyroid ala is invaded by the tumour This patient had a total laryngectomy 9 months following a full course of radiotherapy (5 500 rads Cobalt 60). C = cricoid cartilage E = epiglottis, T = thyroid ala THY = thyroid gland.

not involve the glottic region However they often cross the anterior midline and extend bilaterally above the vocal cords (Coutard & Valat 1927) McGavran et al. (1961) made a distinction between tumours having an "infiltrative margin" and those with "pushing margins" They found the latter more common among supraglottic carcinomas. Bocca et al. (1968) emphasized that the larynx consists of two distinct parts, an upper and a lower part, whose line of demarcation runs at the level of the vocal cord and stressed the different

Table IX. *Multiregional laryngeal carcinoma* (8)
Invasion of cartilage and spread outside the larynx

Invasion of cartilage	
Thyroid	8 (7 through)
Cricoid	6
Arytenoid	6
Epiglottic	1
Spread through	
Cricothyroid membrane	8
Cricothyroid space	7

Table X. *Invasion of pre-epiglottic space (PES) 18 (Laryngeal carcinoma)*

Supraglottic carcinomas		11
Epiglottic	10	
Others	1	
Glottic carcinomas		
Multiregional carcinomas		5

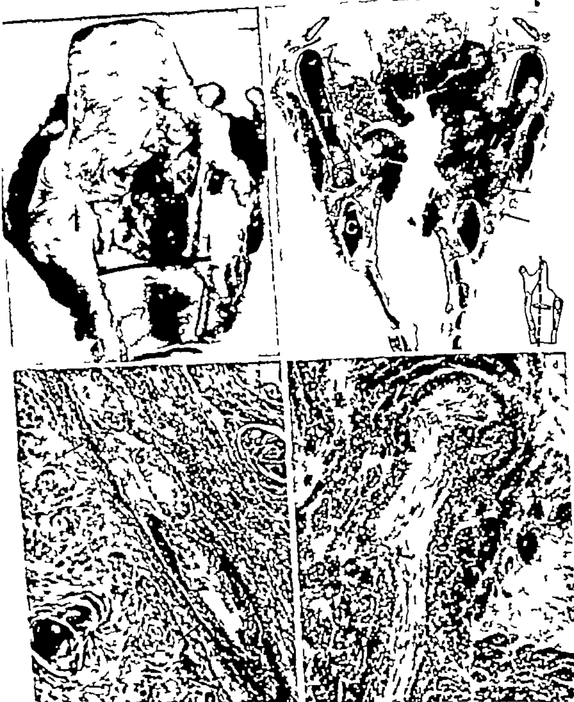


Fig. 19. *Multiregional tumour.* This patient was treated by primary laryngectomy for a large multiregional tumour.

( ) Gross photograph of laryngectomy specimen showing the large ulcerofungating tumour which probably arose at the base of the epiglottis.

(*b*) Coronal section through the laryngectomy specimen at the level of the middle third of the vocal cords. The tumour occupies the epiglottis (E), both false vocal cords, both vocal cords, and extends subglottically. The arrows indicate tumour spreading through the right cricothyroid space and lower part of the right thyroid ala. C: cricoid cartilage. T: thyroid ala.

( ) Photomicrograph illustrating vascular invasion by the tumour. Arrows mark the internal elastic lamina of the arterial wall. (Verhoeff's elastic stain.)

(*d*) Photomicrograph illustrating extensive perineural infiltration by the tumour.



Fig 18 Multiregional tumour with transglottic distribution Coronal section of a total laryngectomy specimen through the middle third of the vocal cords. There is a large tumour with a transglottic distribution occupying the left side of the larynx with subglottic extension The arrows indicate the spread outside the larynx through the cricothyroid space. The lower border of the thyroid ala is invaded by the tumour This patient had a total laryngectomy 9 months following a full course of radiotherapy (5 500 rads Cobalt 60) C = cricoid cartilage E = epiglottis; T = thyroid ala THY = thyroid gland

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Multiregional carcinomas		5









Fig. 19. *Mid regional tumour.* This patient was treated by primary laryngectomy for large multi-regional tumour.

( ) Gross photograph of laryngectomy specimen showing the large ulcerofungating tumour which probably arose at the base of the epiglottis.

(*b*) Coronal section through the laryngectomy specimen at the level of the middle third of the ocal cords. The tumour occupies the epiglottis (E), both false ocal cords, both ocal cords, and extends subglottically. The arrows indicate tumour spreading through the right cricothyroid space and lower part of the right thyroid ala. C = cricoid cartilage. T = thyroid ala.

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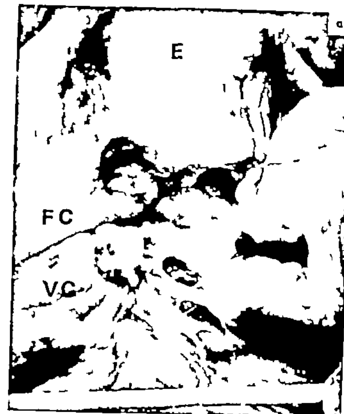








Fig 20 'Multiregional' tumour Five years prior to laryngectomy this patient received a full dose of radiotherapy for a laryngeal carcinoma (in South America)

(*a*) Gross photograph of the anterior commissure region of the total laryngectomy specimen There is a destructive process of the anterior commissure region involving the base of epiglottis (E) the false vocal cords (FC) the vocal cords (VC) and the subglottic region

(*b*) Coronal section of the laryngectomy specimen through the anterior commissure region There is a huge tumour mass occupying both vocal cords and false vocal cords with massive extension outside the thyroid cartilage (T) H = hyoid bone

(*c*) Photomicrograph illustrating extensive tumour invasion of perineural space

(*d*) Coronal section at the level of the middle third of the vocal cords On the right side the tumour has a transglottic distribution and on the left side the tumour involves mainly the glottic region with some extension above the inner angle of the ventricle Note the extensive destruction of the lower margins of thyroid ala bilaterally with penetration through the cricothyroid spaces beyond the laryngeal framework C = cricoid cartilage E = epiglottis T = thyroid ala

Table XI *Fixed vocal cord in laryngeal carcinoma*

	Glottic carcinoma (73)	Supraglottic carcinoma (25)	Subglottic carcinoma (4)	Multiregional carcinoma (8)
Cases with cord fixation	32[a]	1	4	2
Structures invaded.				
Thyroarytenoid muscle	32[a]	1	4	2
Lateral cricoarytenoid muscle	19	—	2	1
Interarytenoid muscle	11	—	1	1
Posterior cricoarytenoid muscle	7	—	1	—
Cricoarytenoid joint	17	—	1	1
Perineural invasion	10	—	2	1
Thyroid cartilage	16	—	2	2
Extension outside larynx	18	—	3	2

4 cases with impaired cord mobility had invasion of the thyroarytenoid muscle only
In the remaining six cases in this group the tumours were so large that movement of the vocal cord could not be assessed

embryologic derivations and different lymphatic supplies. Kirchner & Som (1971) found that exophytic lesions of the supraglottic larynx are the kind that tend to remain confined above the ventricle and the anterior commissure and that these do not invade the thyroid ala. They indicated, however that ulcerative lesions from the supraglottic region may extend downward across the anterior commissure and, when they do so frequently invade and destroy the anterior portion of the laryngeal framework. Hence these authors refer to tumours with this type of infiltrative growth as "transglottic". They make the important observation that microscopic invasion of the thyroid cartilage does not occur unless, at the time of surgery the inferior edge of the growth is visible below the level of the anterior commissure. In our series of 25 tumours, only two invaded the thyroid cartilage and, in one of these, the tumour did extend below the anterior commissure.

Despite these reports, Szlezak (1966) found 10 cases in his series of 25 supraglottic tumours that extended down to or below the glottic region. In our series 24% (6 out of 25) also behaved in this manner. It should be noted, however that both of these latter series deal with highly selected supraglottic tumours with an emphasis on large and/or recurrent neoplasms.

The pre-epiglottic space invasion is very common in this supraglottic group (see Table X) especially among the tumours arising on the epiglottis. Detailed analysis of the invasion of the preepiglottic space and of the nodal metastasis of supraglottic tumours is discussed later (see page 45).

Subglottic carcinoma

The subglottic region is bounded superiorly by the conus elasticus and inferiorly by the lower margin of the cricoid cartilage (Fig. 2). All four tumours that arose in the subglottic region had spread through the conus elasticus to the glottic region, but none of them involved the mucosa of the free margin of the vocal cords (Figs. 16, 17).

Three of the 4 tumours involved both hemilarynges and 2 of these crossed both the anterior and posterior midline. The intrinsic laryngeal muscles were invaded in all four (see Table XI). All four of these tumours had invaded the thyroarytenoid muscle. One had also penetrated the cricotracheal space to involve the posterior cricoarytenoid muscle. The laryngeal cartilages were invaded in 3 of the 4 cases (see Table VIII); the cricoid and thyroid cartilages each were invaded twice and the arytenoid cartilage once.

The tumours extended beyond the larynx in 3 of the 4 cases. In 2 the tumour had









Fig 20 "Multiregional" tumour Five years prior to laryngectomy this patient received a full dose of radiotherapy for a laryngeal carcinoma (in South America).

(*a*) Gross photograph of the anterior commissure region of the total laryngectomy specimen There is a destructive process of the anterior commissure region involving the base of epiglottis (E) the false vocal cords (FC) the vocal cords (VC) and the subglottic region

(*b*) Coronal section of the laryngectomy specimen through the anterior commissure region There is a huge tumour mass occupying both vocal cords and false vocal cords with massive extension outside the thyroid cartilage (T). H = hyoid bone

(*c*) Photomicrograph illustrating extensive tumour invasion of perineural space

(*d*) Coronal section at the level of the middle third of the vocal cords On the right side the tumour has a transglottic distribution and on the left side the tumour involves mainly the glottic region with some extension above the inner angle of the ventricle Note the extensive destruction of the lower margins of thyroid ala bilaterally with penetration through the cricothyroid spaces beyond the laryngeal framework C = cricoid cartilage E = epiglottis, T = thyroid ala.

Table XI *Fixed vocal cord in laryngeal carcinoma*

	Glottic carcinoma (73)	Supraglottic carcinoma (25)	Subglottic carcinoma (4)	Multiregional carcinoma (8)
Cases with cord fixation	32[a]	1	4	+[b]
Structures invaded				
Thyroarytenoid muscle	32[a]	1	4	2
Lateral cricoarytenoid muscle	19	—	2	1
Interarytenoid muscle	11	—	1	1
Posterior cricoarytenoid muscle	7	—	1	—
Cricoarytenoid joint	17	—	1	1
Perineural invasion	10	—	2	1
Thyroid cartilage	16	—	2	2
Extension outside larynx	18	—	3	2

[a] 4 cases with impaired cord mobility had invasion of the thyroarytenoid muscle only
[b] In the remaining six cases in this group, the tumours were so large that movement of the vocal cord could not be assessed.

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Table XII Metastasis to lymph nodes (laryngeal carcinoma)

Carcinomas (110)	Neck dissections (50)	Neck dissections with metastasis to lymph nodes (23)	Metastasis to pre-laryngeal lymph nodes (Delphian) (8)
Glottis (73)	29	9	7[b]
Supraglottic (25)	14	9	
Subglottic (4)	2	1	
Multiregional (8)	5	3 (+1)[a]	1

[a] A single node with metastatic tumour was removed in one patient
[b] 5 of these had neck dissections. 2 of these 5 contained metastatic carcinoma.

extended anteriorly through the cricothyroid membrane and appeared outside the larynx. In one the tumour invaded the upper trachea and extended into the hypopharyngeal submucosa (*vide supra*)

Vascular invasion was observed in 3 cases and perineural invasion in 2. Combined neck dissections were performed in two of the 4 cases—one had positive nodes (Table XII)

Comment The anatomic boundaries of the subglottic region have always been poorly defined Neither the U I C.C nor the A J C. include tumours arising from the undersurface of the vocal cord as subglottic primaries. *Histologically the only structure in this region* that acts as a barrier is the conus elasticus. In keeping with St Clair Thomson (1937) Müller (1955) and Lederman (*1970 1971*) we consider the undersurface of the vocal cord (below the conus elasticus) as part of the subglottic region

St Clair Thomson (1937) noted the tendency of subglottic tumours to spread circumferentially without involving the anterior commissure This tendency was also prominent in our material and occurred in three out of four cases.

Clerf (1940) observed that subglottic lesions often were extensive before laryngeal symptoms occurred.

Baclesse (1949) described the subglottic tumours as flat and irregular with submucosal spread and with ill-defined outlines in contrast to the proliferative supraglottic tumours. Ogura (1955) found most of them "ulcero-fungating Our four cases possess these characteristics and three of them extended down to the lower border of the cricoid cartilage

Ogura (1955) and Kirchner (1969) noted that subglottic tumours frequently invaded cartilage and also that they tended to spread through the cricothyroid membrane Three of our four cases invaded cartilage and two had extended through the cricothyroid membrane

Harrison (1971) stressed the undetectable spread of subglottic carcinoma to the hypopharynx This type of spread occurred in one of our patients.

Multiregional carcinoma

All 8 tumours in this group involved all three laryngeal regions. All eight involved both hemilarynges—eight crossed the anterior midline and three of these also crossed the posterior midline

All 8 tumours invaded many of the *intrinsic* laryngeal muscle groups, and all eight invaded one or more laryngeal cartilages (see Table IX)

The tumour extended beyond the larynx in all eight tumours in this group it penetrated the cricothyroid membrane in all eight the cricothyroid space in seven and the thyroid ala in seven cases (Figs 18 19 20) The tumour had extended into the thyroid gland in three and into the pre-epiglottic space in five (*vide infra*)

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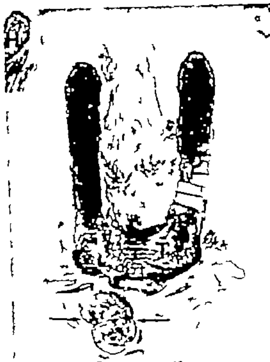




Fig 21 The prelaryngeal (Delphian) lymph node
( ) Coronal section through total laryngectomy specimen illustrating extensive replacement of the prelaryngeal lymph node by metastatic squamous cell carcinoma (arrow) The glottic tumour did not invade the thyroid ala or penetrate the cricothyroid membrane H Hyoid bone, T = thyroid cartilage

(b) Coronal section through the anterior commissure region of total laryngectomy specimen. Note the negative Delphian lymph node (arrow) despite the extensive adjacent tumour which has penetrated the cricothyroid membrane H = hyoid bone T thyroid cartilage.

lymph nodes at the time of laryngectomy In one a single cervical node was sampled and contained metastatic tumour In another the prelaryngeal (Delphian) lymph node in the laryngectomy specimen contained metastatic tumour Five patients had combined neck dissection—three had positive nodes (Table XII).

Comment As one might expect, these very large tumours invade extensively the adjacent structures, spread outside the larynx through multiple exit portals, and frequently have metastasized to lymph nodes at the time of laryngectomy

Pre-epiglottic space invasion

The pre-epiglottic space is that laryngeal compartment bounded posteriorly by the epiglottic cartilage, anteriorly by the thyrohyoid membrane and the hyoid bone, and superiorly by the hyoepiglottic ligament. The lateral parts are in direct continuity with the paraglottic space (Tucker & Smith, 1962).

The body of the epiglottic cartilage is fenestrated and tumours arising on the dorsal aspect of the epiglottis often reach the pre epiglottic space by travelling through these fenestration (dehiscenses) either with or without destruction of the cartilage (Figs. 13 15) Ten of the 15 tumours arising on the epiglottis invaded the pre-epiglottic space either via these fenestrations (Fig. 13) or by destroying the intervening epiglottic cartilage (Fig. 15) (see Table X). One additional supraglottic tumour invaded the pre-epiglottic space from the lateral aspect, without invasion of the epiglottic

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cartilage. Two tumours originating in the glottic region involved the base of the epiglottis with extension into the pre-epiglottic space. Five multiregional tumours also invaded the pre-epiglottic space—four of these involved the dorsal surface of the epiglottis, and the fifth involved the false vocal cord and the aryepiglottic fold

Comment The pre-epiglottic space has been given a number of names in the past among which "space of Boyer is probably the most popular Norris et al. (1970) indicate that Boyer apparently described the prelaryngeal bursa anterior to the thyrohyoid membrane and not the space that we know as pre-epiglottic space

Clerf (1944) stated that the pre-epiglottic space was filled with cellular adipose tissue and contained no lymph nodes but was traversed by numerous lymphatic channels. Dayal et al. (1972) studied this space using dye injections and by dissolving the adipose tissue They could not identify lymph nodes in any of their studies, nor have we been able to identify any lymphoid tissue within the space in any of our serially sectioned specimens.

Of the total 110 laryngeal carcinomas 18 had invaded the pre-epiglottic space All but one of these 18 tumours also involved the dorsal surface of the epiglottis and would therefore be visible to the examining clinician As would be expected, invasion of the pre-epiglottic space was most frequent in the supraglottic tumours, especially those arising on the epiglottis. The pre-epiglottic space was invaded in nearly 70% of our epiglottic tumours and in more than 40% of all supraglottic tumours. These figures are similar to those published by other authors (Ogura, 1955 Szlęzak, 1966 Bocca et al 1968 Kirchner 1969 Norris et al 1970) Whereas it would appear that tumours occupying the anterior commissure could easily spread to the pre epiglottic space such a finding was observed in only two cases in our series

It is necessary to stress that at operation the whole pre-epiglottic space (PES) should be removed in supraglottic carcinomas and in all tumours occupying the dorsal (laryngeal) surface of the epiglottis.

Vocal cord fixation in laryngeal carcinoma

Impaired mobility or fixation of the vocal cords is an important clinical sign in assessing laryngeal tumours. This clinical finding was reported in 39 of the 110 tumours in our series, and was probably present in at least 6 additional cases in the multiregional group As is indicated in Table XI invasion of the thyroarytenoid muscle was present in all 39 cases (Fig 4 9 11 16 20 29). Invasion of other intrinsic muscle groups (Figs. 9 11 20 29) perineural invasion (Fig 20) and invasion of the cricoarytenoid joint (Fig. 11) were less frequently observed, and were thought to be of lesser importance as etiologic factors. In those cases where only vocal cord mobility was impaired there was a lesser degree of invasion (Fig 17). Fixation of the vocal cord indicated invasion of the deeper laryngeal structures—20 tumours invaded or penetrated the thyroid ala and 23 extended outside the laryngeal framework (Figs. 9 11 20 29) Vocal cord fixation as one would expect, occurs most frequently in primary glottic carcinoma. The histopathologic findings in glottic carcinoma with vocal cord fixation have been discussed in detail in an additional paper (Olofsson et al 1973)

Invasion of the thyroid gland

Ogura (1955) noted thyroid gland invasion in 10% of his carcinomas—6 out of 59 (this series included "extrinsic carcinoma" arising in the piriform sinus) Szlęzak (1966) noted thyroid gland invasion in 3 out of 57 cases. Other authors have also reported thyroid gland involvement (Gammarrota 1965) Harrison (1971) advocated removal of the isthmus of the thyroid gland and one or both lobes of the thyroid when dealing with subglottic carcinomas.

There was direct invasion of the thyroid gland in 7 of our cases. In 3 of these, the tumour was classified as "multiregional" and in the remaining four as "glottic" with both supra- and subglottic extension. Metastatic spread to the thyroid gland via either lymphatic or hematogenous route occurred in an eighth case where there was a separate focus of tumour in the lower lobe of the thyroid gland. This tumour, a large glottic lesion with subglottic extension, had invaded the thyroid ala and spread through the cricothyroid membrane.

Metastasis to lymph nodes (Table XII)

Prophylactic neck dissection is not commonly employed in the treatment of laryngeal tumours in Toronto—this procedure is mainly reserved for patients with palpably enlarged cervical nodes. It is performed more frequently in supraglottic tumours and in larger glottic tumours. In our series neck dissections were performed at the time of laryngectomy in 50 out of the 110 laryngeal carcinomas. Twenty-nine were done in the glottic tumours (29 out of 73), 14 in the supraglottic primaries (14 out of 25), 2 in the subglottic group (2 out of 4) and 5 in the multiregional group (5 out of 8). As might be expected, neck dissection was done more commonly in the patients with very large glottic tumours and was actually carried out in 15 out of the 27 glottic tumours with extension outside the laryngeal framework. The incidence of positive cervical nodes was highest in the supraglottic group where 9 out of 14 neck dissections contained metastatic carcinoma. In contrast, only 9 out of 29 neck dissections in the glottic group contained positive nodes, but, in this group we found 5 additional prelaryngeal (Delphian) nodes.

Ogura & Bello (1952) advocated combined laryngectomy and radical neck dissection for advanced carcinoma with or without palpable nodes. In a series of 75 supraglottic carcinomas, in which neck dissection was performed in all patients, Som (1970) found 24 instances of metastasis to cervical nodes—12 were in palpable lymph nodes and 12 in nodes that were not clinically enlarged. Because of the high incidence of clinically undetectable positive nodes, he advocated prophylactic neck dissection in all supraglottic tumours, and so did Surala & Lauerma (1967).

McGavran et al. (1961) in a study of 96 patients with laryngeal tumours, all of whom had neck dissections at the time of laryngectomy, found metastatic tumour in cervical nodes in 52% of transglottic tumours, 33% of supraglottic tumours, and 19% of the infraglottic tumours. Ogura (1955) in a study of 43 patients with laryngeal carcinomas, all of whom had neck dissections at the time of laryngectomy reported 50% (9 out of 18) with positive cervical nodes in the endolaryngeal tumours (arising in vocal cord, ventricle and false vocal cord), and 54% (7 out of 13) in the subglottic tumours, and 58% (7 out of 12) in the supraglottic tumours. The high incidence of positive paratracheal lymph nodes in tumours involving the subglottic area was stressed by Harrison (1971).

Ogura (1955) noted a higher frequency of nodal involvement when the thyroid cartilage was invaded by tumour. Invasion of the thyroid ala is more frequently seen in tumours of glottic origin—it was present in 26 of the 73 glottic tumours in our series. Of these 26, 16 had neck dissection at the time of laryngectomy—7 had positive cervical nodes. An additional 3 had a positive prelaryngeal (Delphian) node. Of the remaining 47 patients with glottic carcinoma, only 13 had neck dissection and, in only 2 did the nodes contain metastatic tumour, though an additional two had positive prelaryngeal (Delphian) nodes (Table XIII).

In the whole series of 110 laryngeal tumours, 38 invaded the thyroid cartilage and, of these 25 had neck dissection—12 had positive cervical nodes, and 4 others had positive prelaryngeal nodes, making a total of 16 out of 38 with positive nodes. In contrast, in those 72 patients with tumours without invasion of the thyroid ala, only 12 had positive

Table XIII *Thyroid cartilage invasion — lymph node metastasis (primary glottic carcinoma (73))*

		Neck dissections performed	Neck dissections with metastasis to lymph nodes
Invasion of the thyroid cartilage	26	16	7 (+3)[a]
No invasion of the thyroid cartilage	47	13	3 (+2)[a]

Additional pos prelaryngeal (Delphian) lymph nodes.

nodes. In 10 of these positive cervical nodes were found in the neck dissection specimens and two other had positive prelaryngeal (Delphian) nodes It should be noted however that in the latter group of 72 cases neck dissections were performed at the time of laryngectomy in only 25

As one would expect, we found a higher *incidence of nodal metastasis in the glottic* carcinomas that had extended outside the laryngeal framework at the time of laryngectomy Of the 27 patients in this group 6 of the 15 neck dissections had positive cervical lymph nodes and 3 more had positive prelaryngeal (Delphian) nodes—a total of 9 out of 27 with positive lymph nodes. In contrast of the 46 patients with tumours confined to the larynx 14 had neck dissections—3 with positive nodes. Two more had positive prelaryngeal lymph nodes, making a total of 5 *out of 46 with nodal metastasis.*

The term Delphian node/s/ was introduced by Cope (1963) dealing with thyroid carcinoma. There is always a lymph node or more to be found just above the thyroid isthmus anterior to the lower portion of the thyroid cartilage This node or group of nodes will be exposed first at surgery and if diseased it will foretell the nature of the disease process to be found in the thyroid gland In only 8 cases in the entire series did the prelaryngeal or Delphian node/s/ contain metastatic tumour (Table XII) All of these tumours involved the subglottic region and in 6 the tumour had spread through the cricothyroid membrane and outside of the laryngeal framework. *In these 6* tumour was found immediately adjacent to the lymph node as well as within the lymph node these nodes could have been involved by *direct extension rather than by lymphatic* spread in some cases. In only two was the primary tumour confined to the larynx In these nodal metastasis was due to spread via lymphatic channels (Fig 21 *a*) In many other cases with large tumours involving the anterior part of the larynx and spread through the cricothyroid membrane we were surprised to see extensive growth adjacent to the prelaryngeal lymph node without involvement of the node (Fig 21 *b*).

In five of the eight cases with positive prelaryngeal lymph nodes neck dissection was performed at the time of laryngectomy metastatic tumour was found in cervical lymph nodes in two of these Ogura (1955) suggested a correlation between positive prelaryngeal and *positive cervical lymph nodes* This was not borne out by our material

The low frequency of prelaryngeal nodal involvement found in our series correlates well with similar findings of McGavran et al. (1961) *It seems that when dealing with laryngeal carcinomas* surgeons have overemphasized the importance of the prelaryngeal lymph nodes.

Ogura (1955) noted that invasion of the *pre-epiglottic space in epiglottic* and aryepiglottic fold carcinomas was associated with a high incidence of metastasis to the cervical lymph nodes. In analysing our supraglottic primary tumours, 7 of the 11 cases with pre*epiglottic space* invasion (Figs. 13 15) had

combined neck dissection—5 had positive nodes. Similarly 7 of 14 without pre-epiglottic space invasion had combined neck dissections —four had positive nodes.

Perineural invasion is associated with a higher rate of nodal metastasis (McGavran et al 1961). Perineural invasion was noted in 20 cases in our series (Figs 19 20). Ten of the 20 had neck dissections—5 had positive nodes. Positive prelaryngeal lymp nodes were found in 5 additional cases.

Vascular invasion was noted in 29 cases in our series (Fig 19). Eleven of these had neck dissections—7 had positive nodes. In three more positive prelaryngeal lymph nodes were found.

Comment It should be noted that the relatively low frequency of combined neck dissection in Toronto does not allow valid comparison of our figures with those from other centres where neck dissection is done on a far greater proportion of patients.

HYPOPHARYNGEAL CARCINOMA (29 CASES)

As in laryngeal carcinomas, we followed the basic U I C C criteria in the hypopharyngeal carcinomas. The classification "multiregional" has been applied to those tumours in which the site of origin could not be determined due to the extreme size or extensive nature of the tumour.

Histologic grading

Using Broders classification (Broders 1932) all the tumours were graded in terms of degree of differentiation (Table XIV).

None of the hypopharyngeal tumours were classified as Grade I, though one tumour with extensive *in situ* carcinoma might be so graded. Twelve tumours were classed as Grade II (this included 5 of the 7 postcricoid tumours). Fourteen were classed as Grade III and two as Grade IV.

Table XIV *Histologic grading of hypopharyngeal carcinomas (Broders')*

	I	II	III	IV	Total
Piriform sinus		6	11	2	19
Postcricoid	1	5	1		7*
Multiregional		1	2		3
Total	1	12	14	2	29

* One *in situ* carcinoma

One of the hypopharyngeal tumours was unusual (Tables XIV and XV). A woman had a partial pharyngectomy for piriform sinus carcinoma when she was 42. Sixteen years later she had 5 500 rads of Cobalt 60 for *in situ* carcinoma in the postcricoid area. Four years later at age 62, she had a laryngopharyngectomy for extensive *in situ* carcinoma of the hypopharyngeal mucosa.

Two patients had radiotherapy for thyroid diseases 30 and 54 years prior to the detection of their hypopharyngeal carcinoma.

Comment A number of authors have pointed out that hypopharyngeal tumours tend to be less well differentiated than laryngeal tumours. Ogura (1955) indicated that Broders Grade III was the predominant tumour in his study of piriform sinus carcinomas. McGavran et al. (1963), in a study of 52 piriform sinus carcinomas, described 21 as being "moderately differentiated" and 31 as being "poorly differentiated". MacComb & Fletcher (1967) referred to laryngeal tumours as being "moderately well differentiated" and hypopharyngeal tumours as being "moderately undifferentiated". Ackerman & del Regato (1970) described hypopharyngeal tumours in general as being "rather undifferentiated" but *did note* that the lesions arising in the retrocricoid area were somewhat better differentiated.

In our own study a much higher proportion of the hypopharyngeal tumours (55%) were poorly differentiated (Grade III or Grade IV) in contrast to the laryngeal tumours where





Fig 22 Piriform sinus carcinoma This patient received a full course of radiotherapy (5 500 rads Cobalt 60) followed by a laryngopharyngectomy and *right neck dissection six weeks later* *Metastatic* carcinoma was present in the cervical lymh nodes.

(*a*) Gross photograph of the laryngopharyngectomy specimen showing the large indurated scarred area occupying the right piriform sinus.

(*b*) Coronal section of the laryngopharyngectomy specimen through the cricoid plate. Note the residual tumour mass (arrows) beneath the extensive submucosal *scarring in the piriform sinus region* A arytenoid cartilage C = cricoid cartilage E epiglottis, T = thyroid cartilage

only 13% were poorly differentiated. In general the postcricoid tumours in our series tended to be better differentiated tumours.

Site of origin and anatomic distribution

Of the 29 cases, 19 arose in the piriform sinus (Figs. 22 23)—14 of these were confined to the piriform sinus one had spread to the mucosa of the postcricoid region and posterior pharyngeal wall and four had extended into the larynx.

Seven of the hypopharyngeal tumours arose in the postcricoid region (Fig 24)—six of these were confined to this region but one had extended to the posterior pharyngeal wall

We could identify no tumours which definitely arose in the posterior pharyngeal wall.

Three of the tumours were classified as multiregional (Figs. 25 26)—one of these probably arose in the postcricoid region (Fig. 26) and the other two probably arose in the piriform sinus (Fig 25) All three tumours involved all three regions, two of them extended into the upper esophagus (Figs. 25 26) and the third extended into the larynx.

Clinical management (see Table XV)

Although the same basic therapeutic categories used in the laryngeal tumours also apply in the hypopharyngeal carcinomas only one of the patients received primary surgery and only 3 patients had surgery for irradiation failure



Fig. 23 Piriform sinus carcinoma. This patient had full course of radiotherapy (5 000 rads Cobalt 60) for left piriform sinus carcinoma. Six weeks later a laryngopharyngectomy and left neck dissection was performed. Metastatic tumour was present in the cervical lymph nodes.

( ) Gross photograph of the left piriform sinus region of the laryngopharyngectomy specimen illustrating the mobile well circumscribed tumour mass (arrows).

(*b*) Horizontal section through the laryngopharyngectomy specimen at the level of the false ocal cords. The tumour (arrows) is well circumscribed and confined to the mucosa and submucosa of the left piriform sinus. A = arytenoid cartilage; FC = false ocal cord, IAM = interarytenoid muscle; T = thyroid cartilage.

Table XV *Clinical management — hypopharyngeal carcinoma (29 patients)*

Site	Primary Surgery (1)	Irradiation Failure (3)	Combined therapy (25)	
			3 000–5 500 R	500–2 000 R
Piriform sinus	1		15	3
Postcricoid		2[a, b]	5	
Posterior pharyngeal wall				
Multiregional		1		2
Total	1	3	20	5
Neck dissections 23 (15)	1 (1)	1 (1)	16 (9)	5 (4)

[a] One patient had a piriform sinus carcinoma successfully treated by radiotherapy She died of postoperative complications following laryngopharyngectomy for a second primary tumour in the postcricoid area.
[b] One patient had a partial pharyngectomy for a piriform sinus carcinoma in 1950. Sixteen years later she received irradiation for carcinoma *in situ* of the hypopharynx. Four years later a laryngopharyngectomy was performed for extensive *in situ* carcinoma of the hypopharynx. No invasive tumour was found in this specimen.

Primary surgery

A non smoking 65-year-old woman who had a large piriform sinus carcinoma was the only patient treated by primary surgical excision This tumour had spread to the postcricoid region and extended into the ipsilateral hemilarynx The tumour had produced vocal cord fixation on that side by invading the intrinsic muscles and the cricoarytenoid joint Tumour had also invaded the thyroid and parathyroid glands and had metastasized to three of the 38 lymph nodes in the combined neck dissection specimen At the same surgical procedure this patient was found to have adenocarcinoma of the stomach which had also metastasized to lymph nodes

Surgery for irradiation failure

Two of the three patients in this category had multiple primary tumours of the hypopharynx (Table XV) Neither had a neck dissection The third patient in this category had a hypopharyngeal tumour treated by 5 000 rads of Cobalt 60 A laryngopharyngectomy was performed 7 months later and revealed a large multiregional tumour extending into the upper esophagus and involving the thyroid gland (Fig. 25) The tumour had metastasized to lymph nodes in the neck and upper mediastinum

Elective surgery following radiotherapy

Twenty five patients were treated by the combined method of therapy—20 received 3 000–5 500 rads of Cobalt 60 followed by elective surgery 6 weeks later five received 500–2 000 rads of Cobalt 60 followed by surgery usually within 48 hours.

Of the 20 patients receiving the full dose of irradiation 15 had *piriform sinus carcinoma* (Figs. 22, 23) and 5 had postcricoid tumours (Fig 24 /3 000 rads/) Neck dissection was performed on 16 and metastatic tumour was found in lymph nodes in 9 of these cases.

Of the 5 patients receiving the partial dose of irradiation followed by immediate surgery

Table XVI *Spread of hypopharyngeal carcinoma (29 cases)*

Invaded structures	Piriform sinus carcinoma (19 cases)	Post cricoid carcinoma (7 cases)	Multiregional carcinoma (3 cases)
Cartilage	11	3	
Thyroid	8		
Cricoid	5	3	
Arytenoid	5		
Epiglottic	1		
Cricoarytenoid joint	3		
Intrinsic laryngeal muscles	8	3	
Posterior crico-arytenoid	5	3	
Interarytenoid	5		
Lateral crico-arytenoid	5	1	
Thyroarytenoid	5	1	
False vocal cord	3		
Pre-epiglottic space	1		
Cricothyroid space (spread through)	4		
Trachea	1	1	
Thyroid gland		1	
Parathyroid gland	1		
Submaxillary salivary gland	1		
Vessel invasion			
Perineural invasion	6		1



Fig. 24. Postcricoid carcinoma. Coronal section through the cricoid plate of laryngopharyngectomy specimen. The tumour outlined by arrows occupies the postcricoid region to the left of the midline. This patient had radiotherapy (3 000 rads Cobalt 60) followed five weeks later by laryngopharyngectomy. A = arytenoid cartilage; C = cricoid cartilage; E = epiglottis; PS = piriform sinus; T = thyroid ala.

3 had piriform sinus tumours and 2 had multiregional lesions (Fig. 26). All 5 had combined neck dissection, and all except one (with a multiregional tumour Fig. 26) had metastatic tumour in the neck nodes.

Spread of hypopharyngeal carcinoma

A characteristic feature of hypopharyngeal carcinomas is extensive submucosal spread (Hiroto 1963, Harrison, 1970). To a large extent the direction of spread and the structures invaded by hypopharyngeal carcinoma is determined by the site of origin of the neoplasm. The structures invaded by the tumours in our series are detailed in Table XVI. The patterns of spread in each of the three hypopharyngeal regions will be discussed separately.

Piriform sinus carcinoma

The piriform sinus is bounded superiorly by the pharyngoepiglottic fold, laterally by the inner surface of the thyroid cartilage, medially by the posterior surface of the aryepiglottic fold and the arytenoid and cricoid cartilages. Inferiorly it extends to the upper edge of the esophagus. In our series, five of the 19 tumours arising in the piriform sinus had extended laterally and appeared outside the laryngeal framework. Four of these penetrated the thyroid ala—this includes three which extended through the cricothyroid space as well—two with involvement of the adjacent thyroid gland. One additional tumour penetrated the cricothyroid space without cartilage involvement.

Of the 19 tumours in our series, 11 had

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Posterior pharyngeal wall				
Multiregional		1		–
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[a] One patient had a piriform sinus carcinoma successfully treated by radiotherapy She died of postoperative complications following laryngopharyngectomy for a second *primary tumour in the postcricoid area*

[b] One patient had a partial pharyngectomy for a piriform sinus carcinoma in 1950 Sixteen years later she received irradiation for carcinoma *in situ* of the hypopharynx. Four years later a laryngopharyngectomy was performed for extensive *in situ* carcinoma of the hypopharynx. No invasive tumour was found in this specimen.

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Of the 20 patients receiving the full dose of irradiation 15 had piriform sinus carcinoma (Figs. 22 23) and 5 had postcricoid tumours (Fig 24 /3 000 rads/) Neck dissection was performed on 16 and metastatic tumour was found in lymph nodes in 9 of these cases.

Of the 5 patients receiving the partial dose of irradiation followed by immediate surgery

Table XVI *Spread of hypopharyngeal carcinoma (29 cases)*

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Cricoid	5	3	
Arytenoid	5		
Epiglottic	1		
Cricoarytenoid joint	3		
Intrinsic laryngeal muscles	8	3	
Posterior crico-arytenoid	5	3	
Interarytenoid	5		
Lateral crico-arytenoid	5	1	
Thyroarytenoid	5	1	
False vocal cord	3		
Pre-epiglottic space	1		
Cricothyroid space (spread through)	4		
Trachea	1	1	
Thyroid gland		1	
Parathyroid gland	1		
Submaxillary salivary gland	1		
Vessel invasion			
Perineural invasion	6		1

b

c

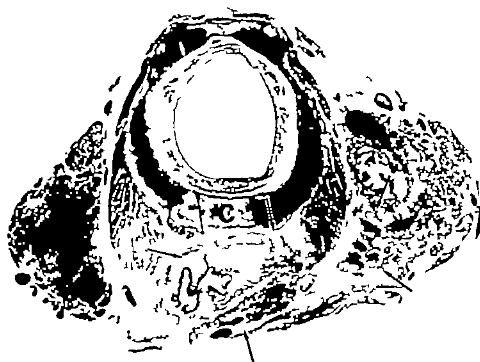


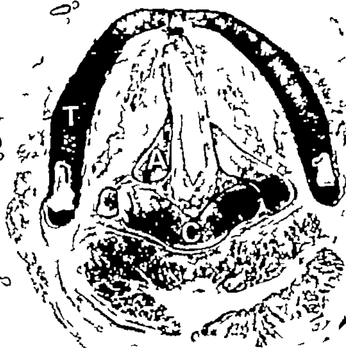


Fig 5 Multiregional hypopharyngeal tumo This patient received full dose radiotherapy (5 000 rads Cobalt 60) followed 7 months later by laryngopharyngooesophagectomy Metastatic carcinoma was present in cervical lymph nodes from both sides of the neck at the time of surgery

(*a*) Gross photograph of the laryngopharyngectomy specimen illustrating two discrete area of mucosal ulceration one in the postericoid region and one in the posterior pharyngeal wall to the right of the midline

(*b*) Horizontal section of the laryngopharyngectomy specimen taken at the level of the ocal cords. The arrows indicate the tumour confined to the mucosa of the posterior pharyngeal wall

) Horizontal section of the laryngopharyngectomy pecimen through the lower part of the cricoid ring Note the extensi e t mour spread (arrows) beneath intact mucosa which ha penetrated through the hypopharyngeal wall to in ade the right lobe of thyroid gland (THY). There is moderate stricture at the level of the cricopharyngeus due to the exten sive fibrous and residual t mour A arytenoid cartilage C = cricoid cartilage T thyroid cartilage


b
T
A
C


T
C

invaded by direct extension one or more of the laryngeal cartilages. Eight of these had invaded the thyroid ala (Fig 22) Invasion of the cricoid and arytenoid cartilage occurred less frequently and invasion of the epiglottic cartilage was observed in only one case It should be noted that in three with extensive involvement the tumour had invaded thyroid cricoid and arytenoid cartilages and that in all three the tumour penetrated into the crico-arytenoid joint space

When piriform sinus tumours extend medially to involve laryngeal structures, laryngeal function may be impaired and this may be the presenting clinical symptom Invasion of the intrinsic laryngeal muscles occurred in 8 piriform sinus carcinomas. Very extensive tumours tended to involve multiple muscle groups. Spread to the false vocal cord was observed in 3 and to the pre-epiglottic space in one The trachea was invaded by one tumour One very extensive tumour invaded the submaxillary salivary gland.

Combined neck dissection was performed in all 19 patients with piriform sinus carcinomas, and in one bilateral dissection was done Metastatic carcinoma was found in cervical nodes in 12 of the 19 Two had vascular and perineural invasion and four more had only perineural invasion

Comment A high proportion of piriform sinus tumours. (11 out of 19 in our series) had invasion of cartilaginous structures. This high frequency probably relates to the lack of anatomic barriers between the piriform sinus mucosa and the invaded cartilaginous structures. Another contributing feature may be the tendency for patients with piriform sinus carcinoma to present late in the course of their disease These same two features may explain the high incidence of intrinsic laryngeal muscle invasion (8 out of 19)

Ogura (1955) observed that piriform sinus tumours tend to be ulcerofungating and found little practical value in separating the tumours



Fig 36 Multiregional hypopharyngeal tumour This patient received a small dose of preoperative irradiation (500 rads Cobalt 60) just prior to laryngopharyngectomy and right neck dissection Despite the very extensive nature of this multiregional hypopharyngeal tumour all 48 cervical lymph nodes were free of metastatic tumour

(*a*) Gross photograph of the postcricoid region of the laryngopharyngectomy specimen illustrating the irregular proliferative fungating surface of the tumour E = epiglottis.

(*b*) Horizontal section through the laryngopharyngectomy specimen at the level of the vocal cords The extensive tumour growth virtually surrounds the hypopharynx but does not penetrate beyond the muscular coat.

(*c*) Horizontal section of the laryngopharyngectomy specimen at the level of the cricoid cartilage The circumferential tumour has spread beyond the muscular coat of the hypopharynx on the right side (arrow) A = arytenoid cartilage C = cricoid cartilage T = thyroid cartilage THY = thyroid gland

Table XVII *Fixed vocal cord in hypopharyngeal carcinoma (9 cases)*

	Piriform sinus carcinoma (6 cases)	Post cricoid carcinoma (3 cases)
Intrinsic laryngeal muscles	6	3
Thyroarytenoid	5	1
Lateral cricoarytenoid	5	1
Interarytenoid	4	
Posterior cricoarytenoid	4	2 (1)[a]
Cricoarytenoid joint	3	
Perineural invasion	4	1

[a] Atrophy of muscle after earlier operation for piriform sinus carcinoma.

vaded this muscle minimally but produced no detectable impairment of vocal-cord function.

Perineural invasion of the recurrent laryngeal nerve was seen fairly frequently in the hypopharyngeal carcinoma group with vocal cord fixation (five of nine), and in one patient with vocal cord fixation this invasion was the main cause

Comment Vocal cord fixation was surprisingly frequent in hypopharyngeal carcinoma. In all nine of the 29 patients with impaired vocal cord function, hoarseness was the predominant symptom it was the earliest symptom in four of these Ogura (1955) noted vocal cord fixation frequently in piriform sinus carcinomas which involved the medial wall Kirchner (1969) made similar observations four of his 24 piriform sinus carcinomas had vocal cord fixation

Metastasis to lymph nodes

As indicated above all 19 of the patients with piriform sinus tumors had neck dissections and 12 had positive cervical nodes at the time of laryngopharyngectomy Only one of the 7 patients with postcricoid tumours had a combined neck dissection and he had metastatic tumour in the cervical nodes All three of those with multiregional tumours had combined neck dissection—two had positive nodes. Thus of 23 of the 29 patients with hypopharyngeal tumour who had combined neck dissection 15 had positive nodes.

A number of authors have noted the high incidence of nodal metastasis in hypopharyngeal carcinoma. Jorgensen (1971) indicated that in his material piriform sinus lesions had the highest incidence of nodal involvement (60%). Harrison (1970) noted that 17 of his 23 patients with piriform sinus carcinoma had positive lymph nodes at the time of surgery

Harrison (1970) in a study of 21 patients with postcricoid carcinomas found 11 with positive nodes at the time of primary surgery (Two patients developed metastasis later) In our own series, infrequency of combined neck dissection in postcricoid carcinomas is striking —one out of seven.

Two explanations are advanced for the high incidence of nodal metastasis in hypopharyngeal tumours. These lesions tend to produce symptoms late and often the symptoms produced are related to laryngeal invasion with fixation of the vocal cord. In contrast to the laryngeal region, the piriform sinuses are richly supplied by lymphatic channels, which converge forward and exit via the lateral orifice of the thyroid membrane and drain into the upper and lower internal jugular chain of lymph nodes (Rouvière 1938 as quoted in MacComb & Fletcher 1967).

The thyroid gland was invaded in five of the 29 cases—three of them via direct extension through the thyroid ala. Ogura (1955) and Harrison (1966–1968) both have commented on the tendency of thyroid gland invasion by hypopharyngeal tumours.

THE EFFECT OF IRRADIATION

The review of 54 tumours from patients who received full-dose radiotherapy (mainly 5 500 rads), at Princess Margaret Hospital, Toronto followed by elective surgery afforded us an unique opportunity to study the patterns of response to irradiation of laryngeal or hypopharyngeal squamous-cell carcinoma.

as to their site of origin within the piriform sinus because most of these tumours involve both the medial and lateral walls. Tumours involving the medial wall tended to invade laryngeal structures producing vocal cord fixation This point was also emphasized by Kirchner (1969) Kirchner also indicated that when laryngeal invasion occurred the tumour often extends into the paraglottic space and then may clinically resemble a laryngeal carcinoma with transglottic distribution When such extension occurs, the tumour may escape through the cricothyroid space All of the above findings were confirmed in our own series.

In comparing the figures in Table XVI with Kirchner's series (1969) of similar tumours, we note that the thyroid cartilage was invaded in about the same frequency but that in our series, the cricoid and arytenoid cartilages and the cricoarytenoid joint space was invaded much more frequently

Harrison (1970) pointed out that tumours of the piriform sinus tend to be diagnosed late and had frequently metastasized to the cervical nodes. Our experiences would tend to confirm this observation.

Postcricoid carcinoma

The postcricoid region the posterior surface of the larynx, extends from the posterior surface of the arytenoid cartilage and its connecting folds to the inferior surface of the cricoid. It is bounded laterally by the piriform sinuses.

As one would expect three of the seven postcricoid tumours had invaded the cricoid cartilage and the posterior cricoarytenoid muscle (Fig 24) One of these was very extensive and involved other muscle groups the trachea and the adjacent thyroid gland.

One of the 7 patients with a postcricoid tumour had combined neck dissection and metastatic tumour was found in the cervical nodes

Vascular and perineural invasion was observed in two and in both the recurrent laryngeal nerve was involved

Posterior pharyngeal wall carcinoma

None of the tumours of this series was considered to have arisen in the posterior pharyngeal wall region.

Multiregional tumours

All three of the large hypopharyngeal tumours, classified as multiregional were characterized by extensive superficial growth and showed little tendency to involve the deeper structures of the larynx. However two of these had extended laterally through the lateral pharyngeal wall to invade the adjacent thyroid gland (Fig. 25 c) One of these patients had a bilateral neck dissection at the time of laryngopharyngectomy and had metastatic tumour on both sides of his neck. One had a neck dissection at the time of laryngopharyngectomy and had a neck dissection on the opposite side at a later date—metastatic tumour was present in lymph nodes in both of these procedures (Fig 25) The third patient who had a unilateral combined neck dissection had negative nodes (Fig 26)

Vocal cord fixation in hypopharyngeal carcinoma

Impaired mobility or fixation of one vocal cord was surprisingly frequent in our series It was noted in 9 of the 29 cases. The causes of this clinical finding are detailed in Table XVII There was interference with the intrinsic laryngeal muscles in all 9 either due to invasion by viable tumour or to fibrous replacement of the muscle after irradiation and eradication of the tumour In 3 piriform sinus tumours, the cricoarytenoid joint was invaded The most common muscle groups invaded were the posterior cricoarytenoid (Fig 24) and the thyroarytenoid Although the thyroarytenoid muscle was invaded as frequently as the posterior cricoarytenoid its involvement tended to be minor Four of the piriform sinus tumours and two of the postcricoid tumours invaded the posterior cricoarytenoid muscle (Fig 24) Another postcricoid tumour had in

Table XVII *Fixed vocal cord in hypopharyngeal* carcinoma (9 cases)

	Piriform sinus carcinoma (6 cases)	Post cricoid carcinoma (3 cases)
Intrinsic laryngeal muscles	6	3
Thyroarytenoid	5	3
Lateral cricoarytenoid	5	1
Interarytenoid	4	
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Atrophy of muscle after earlier operation for piriform sinus carcinoma

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Two explanations are advanced for the high incidence of nodal metastasis in hypopharyngeal tumours. These lesions tend to produce symptoms late and often the symptoms produced are related to laryngeal invasion with fixation of the vocal cord. In contrast to the laryngeal region, the piriform sinuses are richly supplied by lymphatic channels, which converge forward and exit via the lateral orifice of the thyroid membrane and drain into the upper and lower internal jugular chain of lymph nodes (Rouvière 1938 as quoted in MacComb & Fletcher 1967).

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THE EFFECT OF IRRADIATION

The review of 54 tumours from patients who received full-dose radiotherapy (mainly 5 500 rads), at Princess Margaret Hospital, Toronto, followed by elective surgery afforded us an unique opportunity to study the patterns of response to irradiation of laryngeal or hypopharyngeal squamous-cell carcinoma.



Fig 7 No residual tumour following radiotherapy. This patient received a full dose of radiotherapy (5 500 rads Cobalt 60) followed six weeks later by laryngectomy and left neck dissection. There was no metastatic tumour in the cervical lymph nodes.

(*a*) Gross photograph of the laryngectomy specimen illustrating the obliteration of the laryngeal ventricle on the left side.

(*b*) Coronal section of the laryngectomy specimen at the level of the anterior third of the vocal cord. The tumour of the left side of the larynx with a transglottic distribution has been completely

Table XVIII *Response pattern following irradiation*

	No residual tumour	Fibrosis with scattered tumour nests	Minimal tumour response	Residual central tumour
Laryngeal carcinoma (34)	6	12	14	2
Neck dissections	5 (0)	8 (4)	9 (3)	1 (0)
Hypopharyngeal carcinoma (20)	8	7	5	
Neck dissections	8 (5)	4 (2)	4 (2)	

Patterns of tumour response

Full course of radiotherapy

Histologically similar tumours make four distinctly different responses to identical irradiation therapy (Table XVIII) The following patterns were noted in 34 patients with laryngeal and 20 with hypopharyngeal tumours who had the full radiotherapy dose followed by surgery six weeks later

A. *No residual tumour* (Fig. 27) Six of the 34 (18) in whom laryngeal carcinomas were treated by the combined method had no residual tumour in the laryngectomy specimen. Of the six, three had primary glottic tumours (Fig 27) and three had primary supraglottic tumours Five of these six had neck dissection and all were free of metastatic tumour

Of the 20 patients with hypopharyngeal lesions eight (40) had no residual tumour at the primary site at laryngopharyngectomy Seven of these tumours were piriform sinus lesions and one originated in the postericoid region All eight patients had a neck dissection The postericoid tumour and four of the piriform sinus tumour had metastasized to neck nodes at the time of surgery

replaced by fibrous connectiv tissue (arrow) nb obliteration of the laryngeal ventricle Note the joints between the corpus and the major cornua of the hyoid bone (H) C cricoid cartilage T thyroid ala

( ) Photomicrograph to illustrate moderate post-radiation atrophy of the seromucous glands of the submucosa of the false ocal cords

(*d*) Photomicrograph of the scarred area totally replacing the tumour ote the moderate chronic inflammatory infiltrate and the squamous metaplasia of the ducts of the submucosal glands in the upper righ corner

Comment With respect to the primary tumour it was eradicated and replaced by fibrous connective tissue twice as often in the hypopharyngeal as in the laryngeal tumours. However none of the laryngeal tumours had metastasized to the regional nodes at the time of surgery but, in the combined neck dissection specimens, five of the hypopharyngeal tumours (63%) had already spread to the cervical nodes.

B. *Fibrosis with scattered tumour nests* (Fig 28) Twelve of the 34 patients with laryngeal tumours (35%) had extensive fibrosis of the tumour area in which scattered nests of tumour were identified. In the usual pattern of response that we observed tumour nests were scattered evenly throughout the whole of the fibrosed area. In a small number of cases, there were very few tumour nests and these occupied only small portions of the fibrosed area and large areas of fibrosis were free of tumour A main feature in this group was the presence of numerous foreign-body granulomas with giant cells surrounding residual keratin material.

Of the 12 laryngeal lesions, 9 were primary glottic tumours, three were primary supraglottic tumours (Fig. 28). Six neck dissections were performed in the glottic group and two contained metastatic carcinoma. Two neck dissections were performed in the supraglottic group and both were positive.

Seven of the 20 hypopharyngeal tumours (35%) showed scattered nests of tumour in fibrous connective tissue—*four of these were* piriform sinus primaries and three were post cricoid primaries All four patients with piriform sinus tumours had combined neck dissec

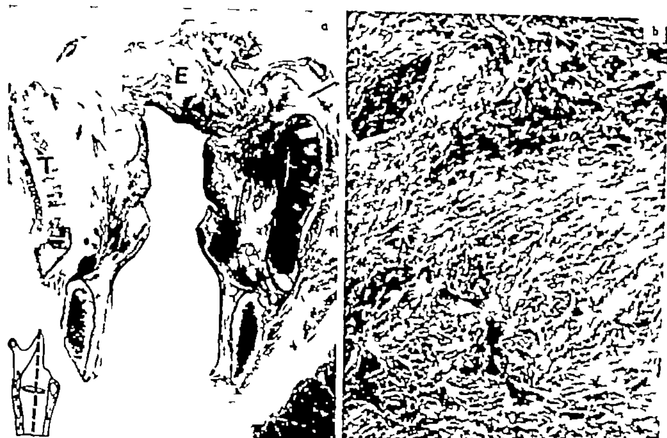


Fig 28 Fibrosis with scattered tumour nests following radiotherapy This patient had a full dose of radiotherapy (5 500 rads Cobalt 60) followed 7 weeks later by laryngectomy and neck dissection. Metastatic carcinoma was found in the cervical lymph nodes.

(*a*) Coronal section from the total laryngectomy specimen at the level of the vocal process. There is extensive fibrosis outlined by the arrows occupying the right aryepiglottic fold and adjacent right piriform sinus. C = cricoid cartilage E = epiglottis; T = thyroid cartilage

(*b*) Photomicrograph from the fibrosed area illustrated in Figure 28 *a* illustrating nests of tumour cells surrounded by dense fibrous connective tissue

tions—two had positive nodes. None of the patients with postcricoid carcinomas had combined neck dissections.

Comment It appears that about one third of laryngeal and one third of hypopharyngeal tumours exhibit fibrosis with scattered tumour nests. In both groups, about one-third of the tumours had metastasized to cervical nodes at the time of surgery

Assessment of the viability of these tumour nests was extremely difficult We attempted to assess the viability of these nests using an autoradiographic technique (Briant et al 1971) after perfusing the whole larynx under hyperbaric conditions immediately after removal from the patient This technique did not prove conclusively whether these nests were viable or not It did, however establish that whole organ perfusion using this method is feasible though technically difficult The technique is no longer used in our laboratory

C *Minimal tumour response* (*Fig 29*). In these tumours (19) there was minimal tumour necrosis and minimal fibrosis. The size of the tumour in the operative specimen corresponded closely to that observed clinically both before radiotherapy and before operation

Fourteen of the 34 laryngeal tumours (41) exhibited minimal response—nine were glottic primaries, 4 were supraglottic and 1 was subglottic *Six neck dissections were performed in* patients in the glottic group—two had positive nodes. Three neck dissections were performed in the supraglottic groups—one had positive nodes. The patient with the subglottic primary did not have a neck dissection

Five of the 20 hypopharyngeal tumours



Fig. 79. *Minimal tumour response to radiotherapy.* This patient had a full dose of radiotherapy (5 500 rads Cobalt 60) followed by laryngectomy and neck dissection. Metastatic carcinoma was present in the cervical lymph nodes.

( ) Coronal section of the total laryngectomy specimen taken through the anterior portion of the arytenoid cartilages. The very large tumour (arrows) occupies the left hemilarynx and partially destroys the arytenoid cartilage (A), thyroid cartilage (T), cricoid cartilage (C), and has spread outside the laryngeal framework through the cricothyroid space. E = epiglottis, THY = thyroid gland.

(*b*) Photomicrograph of the tumour illustrating large clumps of tumour cells with moderate adjacent fibrous connective tissue. A biopsy of the tumour taken prior to the radiotherapy showed an identical histologic pattern.

(25) exhibited minimal response to irradiation—four were piriform sinus primaries and one was postericoid. All four of the piriform sinus lesions had neck dissection— two had positive nodes. The patient with the post cricoid tumour did not have a neck dissection.

Comment. Minimal tumour response was observed nearly twice as often in the laryngeal tumours (41%) as in the hypopharyngeal tumours (25%). Only three of the 14 laryngeal tumours (%) had metastasized at the time of operation while two of the five hypopharyngeal tumours (40%) had done so.

We are convinced that the lack of response to radiotherapy exhibited by these tumours is a manifestation of the biological behaviour of the tumour. Different biochemical characteristics of the tumour seem to influence its radiosensitivity (Tokhadze, 1966; Paavolainen, 1970; Tachibana, 1971).

D. *Residual central tumour.* We hoped that, following radiotherapy the viable tumour would shrink to a small central focus that could be more easily and safely resected by the surgeon. This pattern of response was rarely seen. In only two laryngeal carcinomas was the residual tumour confined to a small focus in the mucosa and submucosa overlying an area of extensive fibrosis. Both of these lesions were glottic primaries. Combined neck dissection was performed on one of these two patients and the cervical nodes were free of tumour.

None of the hypopharyngeal tumours exhibited a central residual tumour.

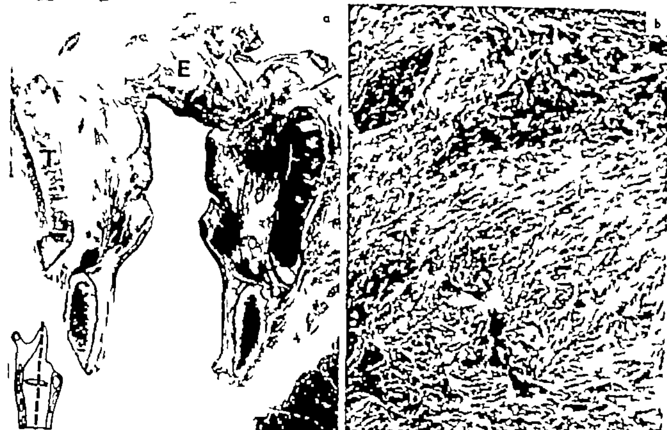


Fig 28 Fibrosis with scattered tumour nests following radiotherapy This patient had a full dose of radiotherapy (5 500 rads Cobalt 60) followed 7 weeks later by laryngectomy and neck dissection Metastatic carcinoma was found in the cervical lymph nodes.

(*a*) Coronal section from the total laryngectomy specimen at the level of the vocal process. There is extensive fibrosis outlined by the arrows occupying the right aryepiglottic fold and adjacent right piriform sinus. C = cricoid cartilage E = epiglottis T = thyroid cartilage.

(*b*) Photomicrograph from the fibrosed area illustrated in Figure 28 a illustrating nests of tumour cells surrounded by dense fibrous connective tissue

tions—two had positive nodes. None of the patients with postcricoid carcinomas had combined neck dissections.

Comment It appears that about one-third of laryngeal and one-third of hypopharyngeal tumours exhibit fibrosis with scattered tumour nests. In both groups about one third of the tumours had metastasized to cervical nodes at the time of surgery

Assessment of the viability of these tumour nests was extremely difficult. We attempted to assess the viability of these nests using an autoradiographic technique (Briant et al 1971) after perfusing the whole larynx under hyperbaric conditions immediately after removal from the patient This technique did not prove conclusively whether these nests were viable or not It did however establish that whole organ perfusion using this method is feasible though technically difficult The technique is no longer used in our laboratory

C. *Minimal tumour response* (*Fig 29*) In these tumours (19) there was minimal tumour necrosis and minimal fibrosis. The size of the tumour in the operative specimen corresponded closely to that observed clinically both before radiotherapy and before operation

Fourteen of the 34 laryngeal tumours (41) exhibited minimal response—nine were glottic primaries, 4 were supraglottic and 1 was subglottic Six neck dissections were performed in patients in the glottic group—two had positive nodes Three neck dissections were performed in the supraglottic groups—one had positive nodes The patient with the subglottic primary did not have a neck dissection.

Five of the 20 hypopharyngeal tumours



Fig. 29. Minimal tumour response to radiotherapy. This patient had full dose of radiotherapy (5 500 rads Cobalt 60) followed by laryngectomy and neck dissection. Metastatic carcinoma was present in the cervical lymph nodes.

(*a*) Coronal section of the total laryngectomy specimen taken through the anterior portion of the arytenoid cartilages. The very large tumour (arrow) occupies the left hemilarynx and partially destroys the arytenoid cartilage (A), thyroid cartilage (T), cricoid cartilage (C), and has spread outside the laryngeal framework through the cricothyroid space. E = epiglottis; THY = thyroid gland.

(*b*) Photomicrograph of the tumour illustrating large clumps of tumour cells with moderate adjacent fibrous connective tissue. A biopsy of the tumour taken prior to the radiotherapy showed an identical histologic pattern.

(25 %) exhibited minimal response to irradiation—four were piriform sinus primaries and one was postcricoid. All four of the piriform sinus lesions had neck dissection— two had positive nodes. The patient with the postcricoid tumour did not have a neck dissection.

Comment. Minimal tumour response was observed nearly twice as often in the laryngeal tumours (41) as in the hypopharyngeal tumours (25). Only three of the 14 laryngeal tumours (21 %) had metastasized at the time of operation while two of the five hypopharyngeal tumours (40 %) had done so.

We are convinced that the lack of response to radiotherapy exhibited by these tumours is a manifestation of the biological behaviour of the tumour. Different biochemical characteristics of the tumour seem to influence its radiosensitivity (Tokhadze 1966, Paavolainen, 1970, Tachibana, 1971).

D. *Residual central tumour.* We hoped that, following radiotherapy the viable tumour would shrink to a small central focus that could be more easily and safely resected by the surgeon. This pattern of response was rarely seen. In only two laryngeal carcinomas was the residual tumour confined to a small focus in the mucosa and submucosa overlying an area of extensive fibrosis. Both of these lesions were glottic primaries. Combined neck dissection was performed on one of these two patients and the cervical nodes were free of tumour.

None of the hypopharyngeal tumours exhibited a central residual tumour.

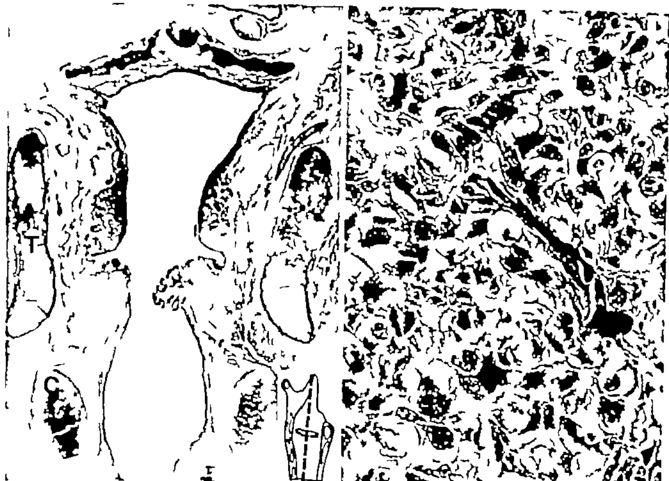


Fig 30 Acute irradiation changes This patient was receiving a full course of radiotherapy for a vocal cord tumour After he had received 3 000 rads of Cobalt 60 he developed thrombosis of his right carotid artery and died

(*a*) Coronal section through the larynx removed at autopsy taken at the level of the middle third of the vocal cords. A well circumscribed tumour mass occupied the free margin of the right vocal cord C = cricoid cartilage E = epiglottis, T = thyroid ala.

(*b*) High power photomicrograph of the tumour illustrating acute irradiation changes. The tumour cell nuclei are irregular in size and shape with many giant forms. There are many "balloon cells" with vacuolated cytoplasm and many pyknotic nuclei

Acute irradiation changes

One patient selected for combined therapy died during irradiation At the time of death he had received a tumour dose of 3 000 rads beginning three weeks before and ending five days before death. At autopsy the tumour showed large areas of necrosis with associated acute inflammatory reaction and surface ulceration The tumour's most striking feature was the extremely bizarre morphology of the individual cells. Balloon cells were common with marked vacuolation of the cytoplasm The nuclei of all the tumour cells tended to be irregular and pyknotic Mitotic figures were numerous and abnormal mitoses were frequent (Fig 30)

Comments The acute effect of irradiation on squamous-cell carcinoma has been well described by authors interested in radiation pathology and need not be elaborated upon here (Rubin & Casarett, 1968 Ackerman & del Regato 1970 Skolnik et al. 1970)

Immediate preoperative irradiation

Nine laryngeal and five hypopharyngeal tumours received immediate preoperative irradiation of 500–2 000 rads In most cases the in

terval between irradiation and operation was 24 to 48 hours In examining the operative specimens from these 14 patients no histopathological features were observed which could be attributed solely to the effects of irradiation

The acute oedema and the early inflammatory response which others described as an immediate reaction to irradiation therapy was not seen in these cases.

Comment As was indicated in the introduction, the rationale of using low-dosage immediate preoperative radiotherapy is to improve the cure rate by achieving a moderate degree of tumour-cell sterilization and by closing off lymphatic channels from the tumour area. This type of therapy does not complicate the surgical procedures nor delay wound healing (Both of these problems are encountered after *full* dose radiotherapy) In animal experiments this type of therapy decreases distant metastasis and local recurrences (Moss & Brand, 1969) Also similar benefits have been recorded in human tumours after this type of therapy (Henschke et al., 1966), but most reports on the clinical side have been inconclusive (Moss & Brand, 1969). Our own cases receiving immediate preoperative radiotherapy exhibited no histopathologic features that distinguished them from those which were operated upon without irradiation.

Comment on the effect of irradiation on the primary tumour

Fifty-four of our patients received full-dose radiotherapy combined with surgical resection six weeks later We hoped that radiotherapy would shrink and sterilize the tumour mass, thus making surgical resection easier and safer Even though in many cases there was significant shrinkage which could be observed clinically scattered foci of tumour cells persisted even in the periphery of such tumours. Such nests were present in 19 of the 54 tumours. Goldman et al (1972), and Skolnik et al (1970) all described a similar response to irradiation. Because of the difficulties to distinguish between nonviable tumour cells and those that are viable and capable of reproduction (Friedman & Goldman 1969 Briant et al., 1971) it is impossible to predict on histologic ground which of these tumours would recur at the primary site. We therefore support the contention of Goldman et al. (1970) that, when operating on such patients, either electively during combined therapy or for irradiation failure all of the tissue previously involved by tumour must be removed. This is particularly important when using partial, voice conservation surgery following irradiation failure. Metastatic spread to neck nodes occurred in about one-third of the patients in the group with fibrosis and scattered tumour nests, and there was no significant difference in the incidence of metastatic spread between laryngeal and hypopharyngeal tumours

The tumour at the primary site was eradicated by irradiation twice as often in the hypopharyngeal as in the laryngeal tumours It should be noted however that the tumours had already spread to the neck nodes at the time of surgery in two thirds of the hypopharyngeal lesions, but not in any of the laryngeal tumours.

Nineteen of the 54 tumours showed minimal tumour response. We were surprised to find that this included more than 40% of laryngeal tumours and 25% of hypopharyngeal tumours. Presumably all of these patients would eventually have required surgery for residual or recurrent tumour at the primary site, if they had not been in the combined therapy program.

The grading (Broders') of the tumours in the pre-operative irradiation group followed the distribution of the whole series. Referring to grading no distinct pattern of response to irradiation could be noted.

Irradiation effect on other tissues

For comparison in the study of irradiation effects we had a number of non-tumour la



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In those patients who received 500 to 2 000 rads with surgery within 48 hours, none of the irradiation effects on other tissues that are described below were observed.

In the single autopsy of the patient who died during radiotherapy we found total atrophy of the hemopoietic elements in the bone marrow cavity but not the epithelial, submucosal gland and vascular changes described below

These changes were found in all patients who received 5 500 rads, either in the combined therapy group or in the irradiation failure group

Epithelial changes

Squamous epithelium is relatively resistant to irradiation change. We have however noted acanthosis and hyperkeratosis much more frequently in the irradiated larynges than in those treated by primary surgery The dysplasia present in the squamous epithelium adjacent to many of the tumours, was not attributed to irradiation effect

The ciliated columnar (respiratory) epithelium is far more susceptible to the effects of irradiation (Alexander 1963 Manara & Mira 1968) Metaplasia of respiratory—type epithelium to stratified squamous epithelium—was frequent especially in the false vocal cords and in the laryngeal ventricles.

Although squamous metaplasia is frequently seen in the false vocal cords of heavy smokers (Auerbach et al. 1970) we have never observed such changes in the laryngeal ventricle in the absence of previous irradiation Despite individual variation the above noted epithelial changes were observed in most of the specimens from both the combined therapy group and the irradiation failure group

Submucosal gland changes

The submucosa of the supraglottic and subglottic regions is rich in seromucinous glands These glands are very susceptible to irradiation and the serous component is more susceptible than the mucinous component (Manara & Mira, 1968 Ackerman, 1972) The glands in our material showed varying degrees of acinar atrophy chronic mononuclear inflammatory infiltration squamous metaplasia of the ductal epithelium and fibrous replacement (Fig. 27 c d) Squamous metaplasia of the ductal epithelium has also been described by Skolnik et al (1970) In the group of cases receiving the combined therapy with full dose of irradiation squamous metaplasia of the ductal epithelium and inflammatory infiltration were prominent In the irradiation failure group acinar atrophy with submucosal fibrosis was more frequent

Blood vessel changes

Important changes occur in the vascular bed following irradiation therapy (Alexander 1963 Manara & Mira 1968 Ackerman 1972) The vascular endothelium is the most susceptible portion of the vessel. Endothelium is vulnerable if the dose of irradiation exceeds 1 700 rads (Alexander 1963) The damage is usually irreversible. Electron microscopy studies have shown "an endothelial swelling and detachment with splitting and swelling of the basement membrane in the subendothelial space and in the media (Ackerman 1972) The endothelial cells undergo dissolution and fibrin thrombi are deposited followed by a complete thrombosis of the lumen and often recanalization at a later date In man the pathognomic sign of radiation effect is the presence of subintimal foam cells in moderate sized vessels (Ackerman 1972)

In our material postirradiation changes were present in both the arteries and the veins —those in the arteries predominating There was no significant difference between the combined therapy group and the irradiation failure group The most prominent and most common change was intimal proliferation with partial obliteration of the lumen More severe damage totally obliterated the lumen and there was recanalization of the arterioles. The vessels

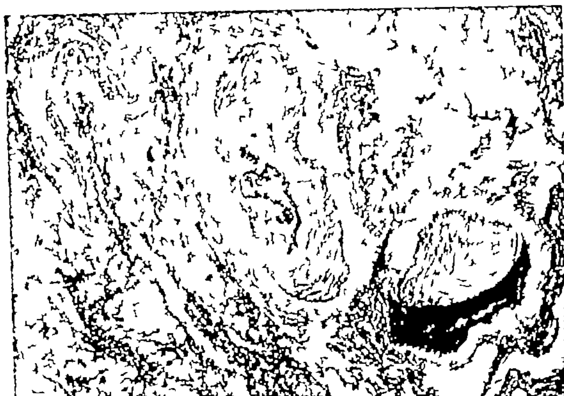


Fig. 31. Post irradiation blood vessel changes. Photomicrograph of prelaryngeal vessels illustrating marked intimal proliferation, splitting of the internal elastic lamina and fibrosis of the adventitia with virtually complete obliteration of the vessel lumen. The patient received full dose of radiotherapy (5 500 rads of Cobalt 60) for carcinoma of the right vocal cord. Seven years later partial laryngectomy was performed for recurrent tumour at the anterior commissure.

containing elastic tissues exhibited varying degrees of fragmentation and replacement of the elastica. Adventitial fibrosis was also common (Fig. 31).

Cartilage changes

There were no gross changes in the cartilaginous framework of the larynx that could be attributed solely to irradiation. Chondronecrosis was occasionally seen in association with infection within the cartilaginous portions of the framework (Fig. 32).

Alexander (1963) noted that in the absence of infection, cartilage shows very little change after irradiation. If the covering of the cartilage remains intact, it resists large doses of irradiation. Many authors, however, have noted that if the perichondrium is breached by operative trauma or tumour invasion, chondronecrosis frequently ensues (Goodrich & Lenz, 1948; Albrecht, 1951; Oeser, 1951; Zange, 1951; Vogel & Bogasch, 1955; Parker, 1962; Rubin & Casarett, 1968). Lederman (1970) noted that a mild perichondritis was occasionally encountered usually after a history of respiratory infection.

Bony changes

In the adult, to a greater or lesser degree, the so-called "cartilages" that make up the laryngeal framework are composed of trabecular bone with marrow containing central portions. This ossification of the thyroid ala, the cricoid and the arytenoids usually follows a specific pattern and has been studied by many radiologists because it has great importance in inter

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Fig 32 Chondronecrosis following radiotherapy This patient received a full course of radiotherapy (5 500 rads of Cobalt 60) for a glottic tumour with subglottic extension Six months later a total laryngectomy was performed for persistent airway obstruction and extensive subglottic oedema.

(*a*) *Coronal section of the total laryngectomy specimen through the posterior third of the vocal cords.* There is extensive destruction of the cricoid cartilage (C) with marked obstruction of the airway by fragments of residual cartilage and granulation tissue (arrows) No residual tumour was found in this specimen.

(*b*) Coronal section of the laryngectomy specimen through the posterior cricoid plate The cricoid cartilage (C) has been largely destroyed and there is *very extensive acute and chronic inflammation as* indicated by the arrows. A = arytenoid cartilage T = thyroid ala, THY = thyroid gland.

pretation of soft tissue films (Scheier 1899 1901–1902 1909 Baclesse 1949) Occasionally especially in the elderly centres of ossification also appear in the cartilaginous tracheal rings.

The changes, which we have seen in the bony portions of laryngectomy specimens can be *attributed to a combination of irradiation* effect and associated infection These changes usually take the form of osteomyelitis with sequestrated bone fragments and a fistulous tract draining to the laryngeal mucosa Similar changes have been described by other authors (Parker 1962 Rubin & Casarett 1968)

Bone marrow changes

The susceptibility of hemopoietic tissues to irradiation is well known and the atrophy of the hemopoietic elements within marrow containing bone is one of the earliest and most predictable signs of even small doses of irradiation (Rubin & Casarett 1968 Ackerman & del Regato 1970)

The marrow spaces in the laryngeal framework of those patients who had no irradiation *contain abundant hemopoietic tissue* All those who received 5 500 rads (including the combined therapy and irradiation failure groups) showed marked atrophy or complete absence of the hemopoietic tissue with replacement by fatty marrow Actual fibrosis of the marrow cavity was seen only in association with tumour *involvement of the adjacent bone In a few cases, residual fragments of active hemo*poietic tissue persisted in the marrow at the margins of the field of irradiation

Muscle changes

Striated muscle is relatively radioresistant. Rubin and Casarett (1968) described secondary changes in striated muscle following oedema, inflammation and vascular disturbance which may be attributed indirectly to irradiation. In addition, Alexander (1963) described fatty degeneration and Zenker's degeneration with hyaline bridges, loss of striation, and scattered or absent nuclei. Manara & Mira (1968) noticed waxy degeneration and fragmentation of single fibers followed by connective tissue proliferation.

These degenerative changes were not observed in our cases. Neurogenic atrophy following operative denervation or tumour invasion of nerve was however not uncommon.

OTHER FINDINGS

Mucosal dysplasia

Dysplastic changes in the laryngeal mucosa varying from mild to moderate to severe to *in situ* carcinoma have long been recognized (Broders, 1932, Altman et al. 1952, Miller & Fisher, 1953, Kleinsasser & Heck, 1959, Holinger & Schild, 1965, Bridger & Nassar, 1971, McNelis & Esparza, 1971). The association of *in situ* carcinoma with an invasive carcinoma either in immediately adjacent mucosa or elsewhere in the larynx has been noted by a number of authors (Snitman, 1945, Brunner, 1950, Miller & Fisher, 1953, Stout, 1953, Kleinsasser & Heck, 1959, Rabbett, 1962, Daly & Valenti, 1969, Miller, 1970).

Dysplastic mucosal changes were present in 14 of our 139 cases—11 in patients with laryngeal carcinoma and three in those with hypopharyngeal carcinoma (Fig. 33). These changes varied from mild focal atypia to widespread severe dysplasia and *in situ* carcinoma. The most severe changes were in the mucosa immediately adjacent to foci of invasive tumor. In seven of the 14 irradiation therapy had been employed four months to three years previously in these; some of the atypia may be attributed to the irradiation.

The presence of multicentric or widespread dysplastic changes within the larynx and hypopharynx may account for the multiple primary malignancies encountered in the laryngeal and hypopharyngeal area. (Wynder et al., 1956, Rabbett, 1962, Heiner, 1967).

In four patients multiple primary squamous carcinomas were present in the laryngeal or hypopharyngeal mucosa—two were laryngeal and two were hypopharyngeal. One of the patients with laryngeal carcinoma had synchronous transglottic and epiglottic tumours, both invasive but with no connections. The other three cases had metachronous tumours.

Other primary malignancies

In addition to noting the high frequency of multiple primary tumours within the larynx and hypopharynx, a number of authors have described laryngeal or hypopharyngeal tumours, associated with other malignancies elsewhere in the body. The association of laryngeal primaries with tumours of the lower respiratory tract and bronchi has been noted by Wynder et al. (1956), Norris (1959), Holinger et al. (1961), Cahan et al. (1962), Knudson et al. (1965), Shaw (1965), Titche (1966), and Auerbach et al. (1970). Shaw (1965) in a study of 306 patients with laryngeal carcinoma found that 23 (7%) had multiple primary malignancies—one third of these in the bronchial tree. In contrast tumours of the hypopharynx seem to be associated more with lesions of the gastrointestinal (GI) tract (Ballantyne, 1967, Stefani & Eells, 1971). Jacobsson (1951) studied 322 patients with hypopharyngeal carcinoma and in the 67 who survived more than two years, 10 developed a second primary tumour—7 of these were in the digestive tract.

Four of the patients in our series had primary tumours outside of the laryngeal—hypopharyngeal area. A previously treated squamous-cell carcinoma of the oral cavity was noted in a patient with piriform sinus carcinoma. Synchronous basal cell carcinoma of the lip and adenocarcinoma of the stomach were present in two patients, both with hypo-

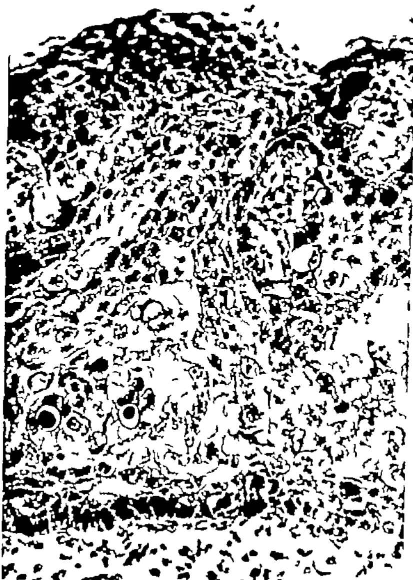


Fig 33 Severe dysplasia and carcinoma-in-situ High power photomicrograph illustrating severe dysplasia and in situ carcinoma This illustration is representative of very widespread in situ carcinoma which was present over large areas of the hypopharyngeal mucosa in a patient who also had two separate invasive carcinomas, one of the postcricoid region and the other of the lateral pharyngeal wall This patient had radiotherapy for thyrotoxicosis 34 years prior to laryngopharyngectomy Metastatic carcinoma was present at the time of surgery in cervical lymph nodes from both sides of the neck

pharyngeal primaries An occult adenocarcinoma of the thyroid gland was discovered in the surgical specimen from a patient with laryngeal carcinoma. With reference to thyroid carcinoma 111 lobes of thyroid gland were removed from 99 patients in this series and we discovered only this solitary occult tumour The incidence of occult carcinoma of the thyroid is said to be much higher than this would suggest (Key 1971)

Anatomic variations

Joints in the hyoid bone Twenty nine patients had a cartilaginous joint space lined by synovium in one or both sides of the hyoid between the corpus and the major cornu (Fig. 27) A few cases of these had an additional joint between the corpus and the minor cornu. This finding was also noted by Goldman et al (1966) in a series of serially sectioned larynges.

Thyroglossal duct remnants. In nine patients, remnants of the thyroglossal duct were present in the prelaryngeal tissues between the thyroid isthmus and the hyoid bone Most remnants showed only microscopic foci of thyroid acini, but the occasional patient had nodules of thyroid parenchyma up to 1 cm in diameter

Thyroid cartilage abnormality Two patients exhibited extreme thickening of one of the thyroid alae but there was no apparent cause for the unilateral hypertrophy

Conclusions

Our knowledge of the anatomy and tumour pathology of the larynx and hypopharynx has been increased by serially sectioned whole organ laryngectomy and laryngopharyngectomy specimens. However we must take into account when drawing our conclusions that we are dealing with a selected material. The majority of our cases were residual and recurrent tumours after previous radiotherapy or were advanced carcinomas treated by preoperative irradiation or in some cases primary surgery A few patients received primary partial laryngectomies for limited carcinomas

The surface extension of the tumours in many cases represents only the top of the iceberg which may explain the great difficulties involved in assessing the tumours—despite careful indirect, and direct laryngoscopy and hypopharyngoscopy supported by radiological examinations Neither of these methods renders accurate information as to the deep extension of the tumours. The difficulties in assessing correctly the extension of tumours are even greater after previous irradiation Post-irradiation oedema, and sometimes an intact overlying mucosa, can totally confuse the picture. Fixation of the structures, and especially vocal-cord fixation, is the main clinical sign of a deep invasion of tumour In a great percentage (over 50) of the cases with vocal-cord fixation, the tumour extended outside the laryngeal framework Therefore we consider vocal-cord fixation a contraindication to partial surgery especially if it occurs after previous radiotherapy In these cases a narrow-field laryngectomy skeletonizing the thyroid cartilage has obvious risks, and wide-field laryngectomy has to be recommended.

The site of origin determines the type of growth and spread of the tumour within the larynx and hypopharynx. The primary glottic tumours extend more often vertically than horizontally The tumours spread mostly outside the larynx through the points of weakness in the laryngeal framework. The glottic tumours spread most frequently outside the larynx at the anterior commissure region through cartilage or when extending subglottically through the cricothyroid membrane In the anterior commissure region the mucosa lies closer to the thyroid cartilage than anywhere else along the cords. There is only a thin layer of submucosa separating the mucosa from the anterior commissure tendon" that intervene with the underlying cartilage. The tumour just as easily spreads downward and out through the cricothyroid membrane.

Many of the larger tumours also spread laterally through the cricothyroid space and through the thyroid ala. This type of spread is prominent for tumours with involvement of both vocal and false vocal cords—"transglottic" distribution. When the cartilages are invaded it is the ossified portions that are first replaced by tumour

Supraglottic tumours are in many cases characterized by pushing margins, a great tendency to invade the pre-epiglottic space (PES) with or without epiglottic cartilage destruction. At operation this space should always be included in the laryngectomy specimen in supraglottic tumours and in all carcinomas occupying the dorsal (laryngeal) surface of the epiglottis. We found that the supraglottic tumours in our material had a strikingly high tendency to invade the glottic region (6 out of 25) which is a factor of great importance, when performing partial supraglottic laryngectomies

The subglottic group of tumours, which was very small, had some common characteristics. They were flat, circumferential and all penetrated the conus elasticus to invade

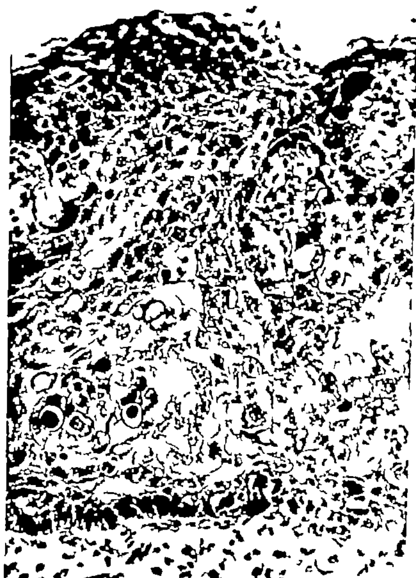


Fig 33 Severe dysplasia and carcinoma in situ High power photomicrograph illustrating severe dysplasia and in situ carcinoma This illustration is representative of very widespread in situ carcinoma which was present over large areas of the hypopharyngeal mucosa in a patient who also had two separate invasive carcinomas, one of the post cricoid region and the other of the lateral pharyngeal wall This patient had radiotherapy for thyrotoxicosis 54 years prior to laryngopharyngectomy Metastatic carcinoma was present at the time of surgery in cervical lymph nodes from both sides of the neck

pharyngeal primaries An occult adenocarcinoma of the thyroid gland was discovered in the surgical specimen from a patient with laryngeal carcinoma. With reference to thyroid carcinoma 111 lobes of thyroid gland were removed from 99 patients in this series and we discovered only this solitary occult tumour The incidence of occult carcinoma of the thyroid is said to be much higher than this would suggest (Key 1971)

Anatomic variations

Joints in the hyoid bone Twenty nine patients had a cartilaginous joint space lined by synovium in one or both sides of the hyoid between the corpus and the major cornu (Fig 27) A few cases of these had an additional joint between the corpus and the minor cornu. This finding was also noted by Goldman et al. (1966) in a series of serially sectioned larynges.

Thyroglossal duct remnants In nine patients, remnants of the thyroglossal duct were present in the prelaryngeal tissues between the thyroid isthmus and the hyoid bone Most remnants showed only microscopic foci of thyroid acini, but the occasional patient had nodules of thyroid parenchyma up to 1 cm in diameter

Thyroid cartilage abnormality Two patients exhibited extreme thickening of one of the thyroid alae but there was no apparent cause for the unilateral hypertrophy

Conclusions

Our knowledge of the anatomy and tumour pathology of the larynx and hypopharynx has been increased by serially sectioned whole organ laryngectomy and laryngopharyngectomy specimens. However we must take into account when drawing our conclusions that we are dealing with a selected material. The majority of our cases were residual and recurrent tumours after previous radiotherapy or were advanced carcinomas treated by preoperative irradiation or in some cases primary surgery A few patients received primary partial laryngectomies for limited carcinomas.

The surface extension of the tumours in many cases represents only the top of the "iceberg" which may explain the great difficulties involved in assessing the tumours—despite careful indirect, and direct laryngoscopy and hypopharyngoscopy supported by radiological examinations Neither of these methods renders accurate information as to the deep extension of the tumours. The difficulties in assessing correctly the extension of tumours are even greater after previous irradiation Post-irradiation oedema, and sometimes an intact overlying mucosa, can totally confuse the picture Fixation of the structures, and especially vocal-cord fixation, is the main clinical sign of a deep invasion of tumour In a great percentage (over 50%) of the cases with vocal-cord fixation, the tumour extended outside the laryngeal framework. Therefore we consider vocal-cord fixation a contraindication to partial surgery especially if it occurs after previous radiotherapy In these cases a narrow-field laryngectomy skeletonizing the thyroid cartilage has obvious risks, and a wide field laryngectomy has to be recommended

The site of origin determines the type of growth and spread of the tumour within the larynx and hypopharynx. The primary glottic tumours extend more often vertically than horizontally The tumours spread mostly outside the larynx through the points of weakness in the laryngeal framework. The glottic tumours spread most frequently outside the larynx at the anterior commissure region through cartilage or when extending subglottically through the cricothyroid membrane. In the anterior commissure region the mucosa lies closer to the thyroid cartilage than anywhere else along the cords There is only a thin layer of submucosa separating the mucosa from the "anterior commissure tendon" that intervene with the underlying cartilage. The tumour just as easily spreads downward and out through the cricothyroid membrane.

Many of the larger tumours also spread laterally through the cricothyroid space and through the thyroid ala. This type of spread is prominent for tumours with involvement of both vocal and false vocal cords—"transglottic" distribution. When the cartilages are invaded it is the ossified portions that are first replaced by tumour

Supraglottic tumours are in many cases characterized by pushing margins, a great tendency to invade the pre-epiglottic space (PES) with or without epiglottic cartilage destruction. At operation this space should always be included in the laryngectomy specimen in supraglottic tumours and in all carcinomas occupying the dorsal (laryngeal) surface of the epiglottis. *We found that the supraglottic tumours in our material had a strikingly high tendency to invade the glottic region (6 out of 25) which is a factor of great importance when performing partial supraglottic laryngectomies.*

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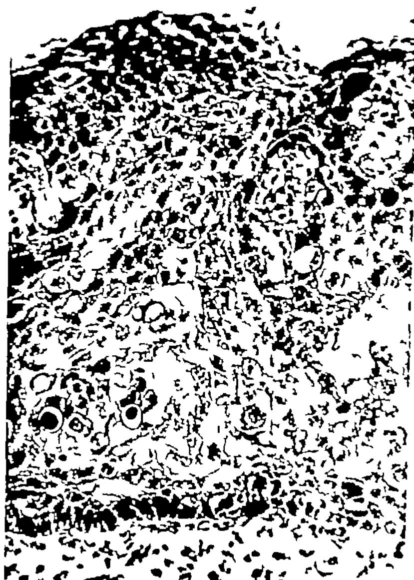


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Thyroid cartilage abnormality Two patients exhibited extreme thickening of one of the thyroid alae but there was no apparent cause for the unilateral hypertrophy

Summary

Whole-organ serial sectioning provides an ideal method of studying the growth and spread of tumour We have used this method to study 139 squamous-cell carcinomas arising in the larynx and hypopharynx—110 in the larynx and 29 in the hypopharynx.

The incidence of laryngeal carcinoma parallels the incidence of malignant tumours arising in the tracheobronchial tree—both are rising Laryngeal tumours tend to be moderately well-differentiated, squamous-cell carcinomas (Broders' grade II) The growth and spread of laryngeal tumours is largely determined by the site of the primary tumour We have made a serious effort to define and delineate the anatomic boundaries as assessed histopathologically of the three regions of the larynx—glottic, supraglottic and subglottic. There are a number of physical (anatomic) barriers within the larynx, which tend to limit the spread of tumour and these form a number of anatomic compartments—the more important ones include Reinke's space pre-epiglottic space (PES) and the paraglottic space.

Seventy-three of the 110 laryngeal tumours arose in the glottic region We consider the conus elasticus to be the histopathological boundary between the glottic and subglottic regions, and the lateral angle of the laryngeal ventricle to be the boundary between the glottic and supraglottic regions. Vertical extension of these tumours (to the supraglottic and/or subglottic regions) occurred much more frequently than horizontal extension (to the opposite hemilarynx) Glottic tumours tend to be confined for long periods by the laryngeal cartilaginous framework. When these tumours spread outside the larynx, they do so through the *points of weakness in the* laryngeal framework. *Tumours involving the* anterior commissure region of the larynx penetrate the cricothyroid membrane after extending subglottically More than 75% of the glottic tumours extending outside the larynx used this portal of exit. These tumours often invade and penetrate the adjacent lower border of the thyroid cartilage. Further posteriorly glottic tumours spread laterally to penetrate the cricothyroid space and extend outside the laryngeal framework. This finding was particularly noted in those large glottic tumours that had extended to the supraglottic and subglottic regions. Here too, the adjacent thyroid ala and upper border of the cricoid cartilage were often invaded and penetrated.

Vocal-cord fixation was a common clinical finding in our series (32 out of the 73 cases with glottic primaries) and we studied the histopathological causes of the fixation. Invasion of the thyroarytenoid muscle was present in all 32, while other structures were invaded less frequently In more than one half of these cases, the tumour had extended outside the laryngeal framework.

Twenty-five of the 110 laryngeal tumours arose in the supraglottic region. Tumours in this region tend to have "pushing" margins One-quarter of these supraglottic tumours extended into the glottic region, *a feature said* to be uncommon. Nearly *one-half of these* tumours invaded the *pre-epiglottic space* (PES), the majority having arisen at the base of the epiglottis *Invasion of the pre-epiglottic space* was an uncommon feature in tumours *arising in* other regions

Only *four of the* 110 laryngeal tumours arose *in the subglottic region.* These tumours *tend to be "ulcerofungating" and present themselves clinically only* when far advanced. They *tend to spread circumferentially and eventually*

the muscles of the vocal cords. These tumours can also invade the hypopharyngeal mucosa through the crico-tracheal space There is then a risk of leaving tumour in this area at the time of surgery and a "recurrence above the stoma may occur

In general the method of whole organ serially sectioning has given the laryngologist much new information concerning growth and spread of laryngeal carcinoma. This information must be transferred into the clinical management of the patients with laryngeal carcinoma. The surgery must be modified according to the extension and type of tumour within the larynx.

Nodal metastasis occurred more frequently in supraglottic carcinomas than in glottic carcinomas It was also more common in larger tumours with destruction of cartilage and spread outside larynx, than for smaller tumours confined to the larynx. The importance of metastasis to the prelaryngeal (Delphian) node/s/ has been overemphasized. Involvement of these nodes occurred less frequently than expected Negative prelaryngeal nodes could be found close to a tumour that had spread outside the larynx

Hypopharyngeal carcinomas are less differentiated than laryngeal carcinomas. Extensive submucosal spread is a characteristic feature of these tumours. Piriform sinus carcinoma was the most common of these tumours and often involved laryngeal structures causing vocal cord fixation The large "multiregional carcinomas had a prominent superficial extension and a comparatively shallower deep extension. Two of the patients with hypopharyngeal carcinomas had received radiotherapy 30 and 54 years earlier for thyroid diseases. These tumours may be considered as irradiation induced carcinomas. There is a great risk involved in treating young/er/ people with radiotherapy Radiation induced tumours may appear usually two or more decades after irradiation Lymph node metastasis were more frequent in hypopharyngeal than in laryngeal carcinomas, which is one of the difficulties involved in the treatment of these tumours.

The study of the effect of preoperative irradiation revealed that different tumours had responded differently to the same type and amount of irradiation Some tumours were totally eradicated and replaced by fibrous connective tissue. In some cases scattered tumour nests were found in fibrous connective tissue and in others, only a minimal tumour response was present. We do not have any centripetal shrinkage of the tumour but islands of tumour can be left in the whole primary area involved. This particular point is of great importance especially when performing partial laryngectomies. The hypopharyngeal tumours were more often totally eradicated than the laryngeal tumours by the same type and dosage of preoperative irradiation. This difference in the response to irradiation must depend upon a difference in the biological behaviour of the tumours.

Irradiation effects were noted on many different tissues as the epithelium submucosal glands and blood vessels. No muscle or cartilage changes were observed The immediate preoperative irradiation did not give any histopathologically visible changes.

A long term follow up of our material will perhaps render further information as to which of the parameters studied have importance for the prognosis of the patients. There is also a great need for improved methods to enable better clinical assessment of the depth and penetration of the tumours. Until better methods of assessment have been developed there are many risks involved in the selecting of patients for partial (voice conservation) surgery especially after previous radiotherapy An increased interest in this field and concentration of the management of these tumours to oncologic centres with intimate collaboration between radiologists and surgeons will afford the patients the best treatment and consequently an increased chance of permanent cure

Zusammenfassung

Serienschnitte von ganzen Organen versorgen uns mit einer idealen Methode das Wachstum und die Ausbreitung der Tumoren zu studieren. Wir haben diese Methode benutzt um 139 Plattenepithelkarzinome in Larynx (110) und in Hypopharynx (29) zu untersuchen. Das Vorkommen von Larynxkarzinomen ist parallel zum Vorkommen von malignen Tumoren in Trachea und Bronchien — das Auftreten von beiden ist im Zuwachs begriffen. Maligne Tumoren des Larynx sind gewöhnlich Plattenepithelkarzinome mit mittelmässiger Differenzierung (Broders Grad II). Das Wachstum und die Ausbreitung von Larynxkarzinomen sind zum grossen Teil von der Lokalisation des ursprünglichen Tumors bestimmt. Wir haben versucht, die histopathologischen Grenzen der folgenden drei Larynxregionen (supraglottische, glottische und subglottische Region) zu definieren und abzugrenzen. Wir finden im Larynx viele anatomische Schranken, die die Tumorausbreitung zu begrenzen vermögen. Diese Schranken bilden mehrere anatomische Abteilungen — die wichtigsten sind das Spatium von Reinke, das prä-epiglottische Spatium (PES) und das paraglottische Spatium. 73 von den 110 Larynxkarzinomen stammten aus der glottischen Region. Wir betrachten den „Conus elasticus" als die histopathologische Grenze zwischen der glottischen und subglottischen Region und den inneren Winkel des Ventriculus laryngis als Grenze zwischen der glottischen und der supraglottischen Region. Vertikale Ausbreitung von glottischen Karzinomen (zur supraglottischen oder subglottischen Region) kommt sehr viel häufiger vor als horizontale Ausbreitung. Glottische Tumoren werden für eine lange Zeit vom knorpeligen Gerüst begrenzt. Wenn diese Karzinome sich aussen am Larynx ausbreiten, wachsen sie durch die schwachen Punkte des Kehlkopfgerüsts. Die Karzinome, die den Commissura anterior umfassen, treten durch die Membrana cricothyreoidea aus, wenn sie sich subglottisch ausbreiten. Mehr als 75% der glottischen Tumoren die sich aussen am Larynx ausgebreitet haben, kommen durch die Membrana cricothyreoidea. Diese Karzinome greifen oft den niedrigen Rand des Schildknorpels an und durchdringen ihn. Weiter rückwärts gelegene glottische Tumoren dehnen sich durch das Spatium cricothyreoideum aussen am Kehlkopfgerüst aus. Dieser Befund wurde besonders in den grösseren Karzinomen mit sub- und supraglottischer Ausbreitung beobachtet. Auch hier war der anliegende Schildknorpel und Ringknorpel angegriffen und durchbrochen worden.

Stimmbandfixierung war in unserer Serie ein gewöhnlicher klinischer Befund (39/110) und wir studierten die histopathologischen Ursachen dieser Fixierung. Der Musculus thyreoarytenoideus war in allen Fällen von Karzinomgeweben durchsetzt. Andere Strukturen sowie andere Muskeln, die Art. cricoarytenoidea und das knorpelige Gerüst waren nicht so häufig angegriffen. Mehr als 50% von diesen Karzinomen hatten sich aussen am knorpeligen Gerüst angesetzt.

25 von 100 Larynxkarzinomen entstanden in der supraglottischen Region. Diese Tumoren weisen im allgemeinen einen schiebenden Rand auf. Ein Viertel dieser supraglottischen Karzinome war in die glottische Region und fast die Hälfte in das prä-epiglottische Spatium (PES) eingedrungen. Die Mehrzahl war an der Basis der Epiglottis entstanden. Das Eindringen von Karzinomgeweben in das präepiglottische Spatium war bei Karzinomen aus anderen Regionen ungewöhnlich.

Nur 4 von den 110 Larynxkarzinomen

involve the glottic region and/or the hypopharynx

Eight of the 110 laryngeal tumours were so large as to defy efforts to categorize them and these were referred to as "multiregional tumours. As would be expected, these tumours invaded many adjacent structures, frequently extended outside the larynx and often had metastasized to the cervical nodes at the time of surgery

In this series, less than 50% of patients with laryngeal carcinoma had a neck dissection at the time of laryngectomy The supraglottic tumours had the highest frequency of nodal metastasis The incidence was higher in those laryngeal tumours that had spread outside the larynx, than in those confined to the larynx. The prelaryngeal (Delphian) lymph node/s/ was involved infrequently by tumour (less than 10%) and when involved, was reached by direct tumour extension (through the cricothyroid membrane) rather than by lymphatic spread. There was no apparent correlation between metastasis in the prelaryngeal and those in the cervical nodes.

The incidence of hypopharyngeal carcinoma parallels the incidence of malignant tumours of the upper gastrointestinal tract (especially those of the oral cavity) rather than those of the upper respiratory tract Hypopharyngeal carcinomas tend to be rather poorly differentiated tumours (Broders grade III)

Two-thirds of the 29 hypopharyngeal carcinomas arose in the piriform sinus one quarter in the postcricoid region and the remainder were multiregional tumours. Extension of tumour beneath intact mucosa was a frequent finding in hypopharyngeal tumours The piriform sinus carcinomas often extended medially to invade laryngeal structures, causing laryngeal symptoms. Extension laterally with invasion of the thyroid ala was also frequently observed

Nearly 80% of the patients with hypopharyngeal carcinoma underwent a neck dissection at the time of laryngopharyngectomy Metastatic tumour was present in 65% of the neck dissection specimens.

In Toronto radiotherapy is a common mode of treatment for laryngeal and hypopharyngeal carcinoma. Only 19 of the 139 patients in this series had primary surgery

In a study of irradiation effect a large number of patients were treated by 5 500 rads Cobalt 60 followed by surgery 6 weeks later Fifty four of these patients are in this present series—34 with laryngeal carcinoma and 20 with hypopharyngeal carcinoma. Four distinct patterns of response to irradiation were seen no residual tumour (14) fibrosis with scattered tumour nests (19) minimal tumour response (19) and residual central tumour (2) Minimal tumour response was much more frequently seen in the laryngeal tumours (41%) than in the hypopharyngeal tumours (25%) In contrast, no residual tumour was present in 40% of the hypopharyngeal tumours, but in only 18% of the laryngeal tumours. It should be noted, however that most of the hypopharyngeal tumours did have positive cervical nodes at the time of operation.

Irradiation effect was also noted on other tissues Hyperkeratosis and acanthosis of the squamous epithelium and metaplasia of the very susceptible respiratory epithelium was a common finding Atrophy of the submucosal glands and typical vessel changes with intimal proliferation splitting of the elastica and fibrosis of the adventitia were other prominent signs of irradiation.

The present material represents only the initial portion of this study A five year follow up of all the patients in this series will allow us to determine which of the many histopathologic features, e g invasion of the thyroid cartilage invasion of the pre-epiglottic space (PES) spread through the cricothyroid membrane or space observed in this study of whole-organ sectioning will have prognostic significance

Nachuntersuchung aller Patienten nach 5 Jahren wird uns feststellen lassen, welche der vielen histopathologischen Befunde, die in dieser Untersuchung vorgelegt wurden (wie Angreifung und Druchdringung des knorpeligen Gerüsts, Ausbreitung durch die Membrana cricothyreoidea, Eindringung in das praepiglottische Spatium usw) eine prognostische Bedeutung haben.

entstammten der subglottischen Region. Diese Tumoren treten geschwürig und wuchernd auf und zeigen sich klinisch erst im fortgeschrit tenen Stadium Sie pflegen die subglottische Region kreisförmig zu umwachsen bisweilen die glottische Region und/oder den Hypopharynx zu umfassen

8 von den 110 Larynxkarzinomen waren so gross, dass unsere Bemühungen sie zu klassifizieren fehlschlugen Diese Karzinome wurden von uns als multiregionale Tumoren be zeichnet. Wie erwartet umfassten diese Tu moren viele angrenzende Strukturen und breiteten sich häufig aussen am Larynx aus und waren zur Zeit der Operation auch an den regionalen Lymphknoten metastasiert.

In dieser Serie hatten weniger als 50% der Patienten mit Larynxkarzinomen eine radikale Halslymphknotenausräumung zur Zeit der Operation. Die supraglottischen Karzinome hatten die höchste Frequenz von Lymphknoten metastasen Die Frequenz von Lymphknotenmetastasen bei Tumoren die sich aussen am Larynx ausgebreitet hatten war höher als bei Tumoren die im Larynx begrenzt waren Der prä laryngeale Lymphknoten (Delphian Lymphknoten) war selten von Tumoren angegriffen (in weniger als 10%) und wenn es der Fall war meistens durch direkte Karzinomausdehnung und nicht durch lymphatische Ausbreitung Wir fanden keine sichtbare Be ziehung zwischen Metastasen in den prä-laryngealen Lymphknoten und Metastasen in den Halslymphknoten

Die Häufigkeit des Vorkommens von Hypopharynxkarzinomen *verläuft parallel mit* der von malignen Tumoren in den Mund und oberen Magen Darm Bereichen, nicht aber der von Luftwegskarzinomen. Hypopharynx karzinome sind gewohnlich Plattenepithelkar zinome mit schlechter Differenzierung (Broders Grad III)

Zweidrittel von den 29 Hypopharynxkarzinomen waren im Sinus piriformis entstanden ein Viertel in der Postcricoid Region und die übrigen wurden von uns als multiregionale Tumoren bezeichnet. Ausbreitung von Hypopharynxkarzinomen unter einer unverletzten Schleimhaut wurde häufig festgestellt. Die Tumoren des Sinus piriformis breiteten sich oft medial aus, drangen in die laryngealen Struk turen ein und verursachten laryngeal Symptome Laterale Ausbreitung mit Eindringen in den Schildknorpel wurde auch häufig beobach tet

Fast 80% der Patienten mit Hypopharynx karzinomen hatten eine radikale Halslymph knoten Ausräumung zur Zeit der Laryngohypopharyngektomie 65% von den Fällen mit radikaler Halslymphknoten Ausräumung hatten Metastasen in den Lymphknoten

In Toronto ist Strahlentherapie eine gewöhn liche Methode zur Behandlung von Larynx und Hypopharynxkarzinomen. Nur 19 von den 139 Patienten in dieser Serie hatten eine chirurgische Erstbehandlung erhalten.

In einer Untersuchung über die Wirkung der Strahlentherapie war eine grosse Zahl von Patienten mit 5 500 Rads Cobolt 60 bestrahlt worden die Operation erfolgte sechs Wochen später 54 der so behandelten Patienten wur den von uns untersucht — 34 mit Larynx karzinomen und 20 mit Hypopharynxkarzinomen Vier ausgeprägte Reaktionsmuster wurden beobachtet 14 ohne Residualkarzi nome 19 mit zerstreuten Tumorresten im Bindegewebe 19 mit minimaler Tumorreak tion und 2 mit einem Tumorrest im Zentrum Minimale Tumorreaktion auf Bestrahlung war in Larynxtumoren viel häufiger (41%) als in Hypopharynxtumoren (25%) Im Gegensatz dazu hatten 40% der Hypopharynxkarzinome *keine Residualkarzinome* und nur 18% der Larynxkarzinome Es wurde festgestellt dass die meisten der Hypopharynxtumoren zur Zeit der Operationen an den Halslymphknoten metastasiert waren

Andere Gewebe zeigten auch postradiologische Veränderungen wie Metaplasie der Zylinderepithel, Atrophie von submukosen Drüsen und Verdickung der Intima und Fibrose der Adventitia der Gefässe.

Das vorliegende Material stellt nur den initialen Teil dieser Untersuchung dar Eine

Nachuntersuchung aller Patienten nach 5 Jahren wird uns feststellen lassen, welche der vielen histopathologischen Befunde die in dieser Untersuchung vorgelegt wurden (wie Angreifung und Druchdringung des knorpeligen Gerüsts, Ausbreitung durch die Membrana cricothyreoidea, Eindringung in das präepiglottische Spatium usw.) eine prognostische Bedeutung haben.

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A Clinico-Pathological and Anatomical Study of Temporal Bones and Brain Structures

BY

CARL CHRISTIAN HANSEN M.D

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PREFACE

The studies presented here were elaborated over a period of 11 years (1960–1971) during appointments in departments and institutes connected with The University of Aarhus, The University of Southern California, and The University of Odense.

The encouragement to commence working with the complicated subject – the aetiology of perceptive deafness came from Ole Bentzen, M.D., Ph.D. The State Hearing Rehabilitation Centre, Aarhus, who during my time in his department, and later on, inspired me and supported the efforts. For all this I am in great debt of gratitude. Audiometry Technician, Mrs. Annie Jentsch gave me able assistance in performing many of the audiometric evaluations, for which I extend my sincere thanks.

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INDEX

PREVIOUS PUBLICATIONS

The study here submitted represents abstracts of the following treatises:

A. Cortical hearing loss in a patient with glioblastoma. Neuropathological analysis of a case. *Arch Otolaryng* 1963 *77* 461 (In collaboration with Edith Reske Nielsen).

B. Pathological studies in presbycusis. Cochlear and central findings in 12 aged patients. *Arch. Otolaryng* 1965 *8* 115 (In collaboration with Edith Reske Nielsen).

C. Pathological studies in perceptive deafness. A patient with hydrops of the labyrinth *Acta oto-laryng* (Stockh.) 1963 *suppl 188*. 162. (In collaboration with Edith Reske-Nielsen).

D Vascular anatomy of the human temporal bone. A preliminary report. *Ann. Otol (St Louis)* 1970 *79* 269

E. Vascular anatomy of the human temporal bone I. Anastomoses between the membraneous labyrinth and its bony capsule. *Arch Klin. exp Ohr Nas u. Kehlk. Heilk.* 1971 *200* 83

F Vascular anatomy of the human temporal bone II. Vascular anastomoses inside the labyrinthine capsule. *Arch. Klin. exp Ohr-, Nas. u Kehlk Heilk 1971 200 99*

G Vascular anatomy of the human temporal bone III The vascularization of the vestibulo-cochlear nerve. *Arch Klin exp Ohr Nas u Kehlk Heilk* 1971 *200* 115

INTRODUCTION

According to the relevant literature the aetiology of perceptive hearing loss, especially the loss experienced late in life has been explained as a lesion involving peripheral as well as central sites in the auditory system. So far however systematic studies including a correlation of the clinical and pathological findings in the peripheral auditory organ have failed to demonstrate any parallelism between the degenerative changes involving the internal ear and the diagnosed loss of hearing (*Sporleder* 1899 *Crowe et al* 1934 *Saxén* 1952 *Schuknecht* 1955). Consequently these authors held that the aetiology of this type of hearing loss might include changes due to age in the cerebral auditory pathways and centres. *Matzker* (1958) and *Kirikae et al.* (1964) for instance have observed such changes in the brain stem. Unfortunately comparative studies of peripheral and central lesions in patients with well-defined perceptive deafness are not available

During my term, from 1959 to 1960 in Statens Hørecentral in Arhus (The State Hearing Centre in Arhus (Head. O Bentzen, M.D Ph D)) I was inspired to embark on such a comparative clinico-pathological study of structures in temporal bones and brains. In patients whose past medical histories included episodes of heart failure or sequelae of cerebral apoplexy the hearing loss seemed to be of a degree more severe than that otherwise observed in healthy individuals at equivalent ages In the course of the ensuing study the audiometric findings were evaluated and the degrees of the arteriosclerotic cerebral changes were determined the study included bilateral arteriography of carotid vessels as well (performed in the Neurosurgical Department G of Arhus Kommunehospital (University Clinic in Arhus) (Head. R. Malmros, M.D Ph D)) On the basis of these tests the severity of the cerebral lesions was found to be almost directly proportional to the hearing losses diagnosed by pure-tone audiometry According to these purely clinical, preliminary studies (*Hansen*, 1961) it seemed as if hearing losses which develop late in life might be attributable to cerebral lesions. The author found it worth consideration to compare structures in temporal bones and brains and hence exposed two groups of patients to audiometric examination, namely one group comprising 100 patients above the age of 65 years, and one group comprising 50 patients in the age group 20 to 60 years – unpublished data. Autopsy was performed in 14 cases, and the temporal bones and brains excised on these occasions were exposed to study The findings are discussed in Part I of the present monograph.

Gross inspection and microscopy of the brains were performed by Edith Reske Nielsen, M.D Ph.D Head of the Department of Neuropathology University Hospital, University of Arhus.

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PART 2. *Studies of Vessels in Temporal Bones After Injection of Contrast Medium* 47

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PART 1

Clinical and Pathological Studies

The subject matter of Part 1 is the histological study of temporal bones and brains from patients who have been exposed to pure-tone audiometry with a view to amplifying our present insight into the pathological basis of perceptive hearing loss associated with old age

Chapters I II, III IV and V are abstracts of treatises A, B and C.

various sections of the auditory system disclosed obvious discrepancies For instance the arterial system in the base of the skull might occasionally be a site of severe arteriosclerotic changes—even occlusion of the vascular lumen— while vessels as well as neural elements in the labyrinth apparently remained normal. This, however is hardly compatible with the general concept according to which arteries of the labyrinth are end arteries By means of injections of contrast matter the author tried consequently to clarify whether there might be a vascular connection between extracranical vessels via the osseous structures of the labyrinth to the vascular system in the labyrinth in excess of the supply to the peripheral hearing organ via intracranial vessels

The techniques used for such experimental injections into 43 temporal bones from man were elaborated by the author The series comprise temporal bones derived from senile patients as well as from much younger individuals

The findings obtained in these experiments are discussed in Part 2 of the present monograph

On the initiative of and in collaboration with William F House M D Otologic Medical Group Los Angeles the first part of the study was commenced It was supported by grants from the University of Southern California, Department of Otolaryngology (Head Aldon Miller M D) and the Otological Medical Foundation in Los Angeles (Head Howard P House M.D) Later the project has been completed in the Institute of Anatomy Odense University (Head F Bierring, M.D) One detail of practical interest (item 11 page 79) for the elaboration of the celloidine technique by which to study injected specimens was elaborated in cooperation with Antonio Mazzoni, M.D., Ferrara Italy who joined the laboratory one year after its establishment. Furthermore, he injected one colour 'microphil into ten of the temporal bones used for this study

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PART 1

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CHAPTER I

Material and Methods

The series comprise a total of 14 patients who are classified into the following groups:

A 43-year-old patient with cerebral tumour and fluctuating hearing capacity treatise A. "Cortical hearing loss in a patient with glioblastoma

Twelve senile patients, all of whom except one were above the age of 65 years treatise B "Pathological studies in presbycusis. Cochlear and central findings in 12 aged patients"

One 65-year-old patient with Ménière's syndrome treatise C. "Pathological studies in perceptive deafness. A patient with hydrops of the labyrinth

The techniques used for post-mortem inspection of brains and temporal bones and for the preparation of the histological specimens were identical in the three cited studies.

The patients were hospitalized in Århus Kommunehospital (University Clinic in Århus) or in departments attached, and died there during the period from 1961 to 1963 They had all been carefully examined, clinically as well as otologically pure-tone audiometry at frequencies of 250 500 1000 2000 4000, and 8000 cycles per second had been performed in all cases.

Organs and brains from all patients were inspected and the temporal bones were excised

The temporal bones were fixed in 4 / neutral formalin for at least one week and forwarded to the Temporal bone Laboratory of Professor H. K. Kristensen, Rigshospitalet (University Clinic, Copenhagen) Using the technique recommended by *Kristensen* (1949), the preparations were decalcified for about four or five months in a buffer solution composed of equal portions of 8 n formic acid and 1 n sodium formate, pH 2.2. The decalcified specimens were embedded in celloidin *and cut in the horizontal plane in serial sections, the thickness of 15 micron.*

Every 10th section was stained with Ehrlich's haematoxylin-eosin. Selected sections were exposed to the following specific stains: Nissl-substance stain using Anthracene blue pH 2, myelin sheath stain combined with connective tissue stain according to Kultschitzky + van Gieson axis cylinder stain, using Bodian's method and periodic acid-Schiff (PAS) according to McManus.

The brains were fixed for at least three weeks in 4 • neutral formalin.

A central block comprising cerebrum, brain stem, and cerebellum was removed in order to follow the acoustic pathways histologically Anteriorly the block was limited by the optic chiasm, laterally by the hippocampal gyri, and posteriorly by the cerebellum.

In the course of dissection of the block, the following regions were selected with special reference to a study of the acoustic pathways and nuclei.

1 The site of transition between the pons and the medulla oblongata, including the acoustic nerves
2. The pons at the site of the trigeminal nerves.
3 The mesencephalon, including the inferior colliculus.
4 The upper portion of the mesencephalon, including the medial geniculate body
5 Matter from both auditory centres the transverse gyri and the central portion of the superior temporal gyrus, together with
6 Supplementary tissue specimens from other parts of the brain beyond the auditory pathways and centres

The specimens were cut in sections, the thickness of 7 micron.

In excess of the routine stains such as haematoxylin-eosin, van Gieson, gallocyanin-chromalum (Einarson) and Mahon, the following specific stains were used axis cylinder stain according to Davenport modified McManus stain and toluidine blue

Note. If not otherwise stated the figures are designated in accordance with those in the treatises.

CHAPTER II

Neuropathological Analysis of the Temporal Bone and the Brain in a Patient with Glioblastoma and Fluctuating Hearing Capacity

According to a series of previously published studies (*Grahe* 1932 *Brunner* 1935 *Walker* 1951 *Nielsen & Berryman*, 1952 *Saltzman* 1952 *Drake & Mc Kenzie* 1953 *Greiner et al.*, 1953 1956 *Spiegel & Wycis* 1953 *Thiébaut et al.*, 1957 *Wycis et al.*, 1958 *Bentzen* 1961) audition of pure tones may vary parallel with pathological changes in the brain.

The present chapter which is a synopsis of treatise A, outlines briefly the most important data in the case history together with the clinical findings, in particular the audiometric findings, in a 43-year-old man whose hearing fluctuated parallel with pathological processes in the brain the lesions were partly attributable to the neurosurgical measures performed. The patient died of pulmonary embolism. The most important pathological findings are discussed and an attempt is made to have the clinical and pathological findings correlated.

The patient was admitted to the neurosurgical department G in November 1959 on account of progressing headaches associated with pressure exacerbation and explosive vomiting The clinical examination failed to reveal any anomalies. Papillary oedema of 1 dioptre and haemorrhages of a marbled pattern involving the background of the eye were manifest.

Audiometry of the 43-year-old patient showed that his hearing still was normal (fig 1)

The caloric reactions to irrigation with water at 30° C were normal. Ventriculography disclosed a space-filling process anteriorly in the right cerebral hemisphere and surgery exposed a tumour, measuring about 3 × 8 × 6 cm, in the posterior portion of the frontal region to the right, it was questionable whether surgery had been sufficiently radical at medial and profound sites towards the basal ganglia. The histological diagnosis was established as. glioblastoma (signed, Edith Reske-Nielsen)

Four days after surgery the patient managed to co-operate satisfactorily at the audiometry carried out in the ward The audiogram (fig. 1 corresponding to fig. 2 in treatise A) was comparable with that of a "presbycousis hearing curve obtained in cases of 75-year-old patients, according to the standard established by *Johansen* (1943) At this stage, a moderate, left-sided, central facial paresis occurred together with slight paresis of the left arm.

Six days after surgery audiometry was repeated. The patient's hearing had improved a little (fig. 1 corresponding to fig. 4 in treatise A)

In the course of dissection of the block, the following regions were selected with special reference to a study of the acoustic pathways and nuclei.

1 The site of transition between the pons and the medulla oblongata, including the acoustic nerves
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Fig. 2. Hearing curves depicting the fluctuating audition, bilaterally symmetrical, in the patient discussed in chapter II. (1) Curve obtained by audiometry carried out in the patient's home (dashed line). (2) curve obtained prior to the second surgical intervention indicated by the tumour (fully drawn line). (3) curve obtained while cerebral oedema, provoked by the repeated surgery, was in evidence (dotted line).

Ophthalmological examination on the same day revealed papillary oedema of 2 dioptres on both eyes.

The patient died suddenly two days after the last audiometric examination.

Immediately upon death, the brain was fixed *in situ* in a 4 % solution of neutral formalin.

Post-mortem inspection of the organs revealed a large pulmonary embolism, but otherwise normal findings.

The brain and the left temporal bone were removed.

Microscopy of the left temporal bone: normal conditions (cf. treatise A).

Gross inspection of the brain. A defect, measuring 8 × 8 × 6 cm, was demonstrable in the right frontal lobe, extending upwards into the adjoining portion of the right temporal lobe which was lined by brain tissue infiltrated by the tumour. The infiltration spread to the striate bodies, the internal capsule, and the anterior portion of the right thalamus. Through the corpus callosum the growth penetrated into the left frontal lobe at which site the infiltration extended medially and in front of the anterior horn.

Microscopy of the brain. The histological findings in the acoustic pathways, the nuclei, and in the cortical hearing centres have been discussed in detail in treatise A and consequently the pathological findings shall merely be outlined here, classified according to degrees of severity; also the influence of the latter on the hearing is evaluated.

I. Chronic lesions which are presumed to suppress completely functions in the regions concerned.

1. Malacias localized to the right cortical hearing centre.
2. Disappearance and degeneration of the white substance in the right temporal lobe.
3. Atrophy and degeneration of the right inferior colliculus.
4. Right-sided chronic degeneration of the white substance in the brain stem.

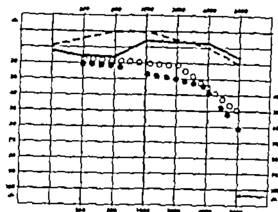


Fig 1 Hearing curves depicting the fluctuating audition, bilaterally symmetrical, in the patient discussed in chapter II.

Fully drawn line	= prior to	first surgical intervention
Dotted line,	= four days after	– – –
Circles,	= six days after	– – –
Dashed line,	= five months after	– – –

Five months later the patient was seen in his own home in order to have an audiometric follow-up He felt quite well and it was his intention to resume work His only complaint was som trouble with the fingers of his left hand which he was unable to control The audiogram showed normal conditions (dashed line in figs. 1 and 2, corresponding to fig. 6 in treatise A)

Eight months and two weeks after surgery the patient was re admitted to the department on account of a moderate loss of strength in the left extremities and an increased demand for sleep The patient did not realize his own condition in particular he did not complain of hearing failure

Clinical symptoms involving the right side of the brain were demonstrable Bilateral arteriography of the carotid arteries revealed recurrence of the tumour in the right cerebral hemisphere and ingrowth into the left cerebral hemisphere Ophthalmological examination showed papillary oedema of 2 dioptres while the otological findings were normal According to the audiogram, his hearing had deteriorated during the three month interval particularly his perception of tones in the high-frequency range (fig. 2, corresponding to fig 7 in treatise A)

Partial removal of the glioblastoma was performed, including resection of the entire frontal lobe on the right side and excision of large quantities of tumour tissue at the site of the foremost parietal lobe but radical surgery was not practicable

Transistorized audiometry was carried out in the ward 12 days after surgery on which occasion the patient managed to co-operate satisfactorily (fig 2, corresponding to fig 8 in treatise A) although he was still somewhat apathetic. The curve depicting the symmetrical hearing loss was found to equal that otherwise obtained in cases of 75-year-old patients, according to the standard established by *Johansen* (1943) In fact, the patient's hearing was just as good as it had been when he, eight months earlier had been suffering from cerebral oedema (figs 1 and 2)

loss. In the cases described by *Sérieux & Mignot* (1901) and by *Bramwell* (1927), post-mortem inspection of the brains exposed extensive destructive changes in the temporal lobes on either side. The patient described by *Mott* (1907) presented severe lesions localized to all transverse gyri, including the white substance on one side, while the pathological changes in the other hemisphere exclusively were localized to the cortex in the hearing centre. *Misch* (1928) observed that the lesion in his patient was localized only to the anteromedian part of the superior temporal gyrus of one hemisphere while the transverse gyri on the other side were totally destroyed. Finally the extensive pathological, bilateral changes in the internal capsules involved also the acoustic radiation. In contrast, the cerebral cortex was found to remain normal in the deaf patient described by *Clark & Russell* (1938).

The above cited studies seem to indicate that the hearing capacity in man remains uninfluenced by unilateral hemispheric lesions whereas it will be extinct in patients in whom destructions involve the acoustic areas in both cerebral hemispheres. In the patient here discussed, the destruction of the right hearing centre may have been due to the severe oedema previously provoked by the tumour which involved the right cerebral hemisphere. Furthermore, ingrowth of the tumour into the right internal capsule may have been responsible for the severe right-sided, chronic degeneration of the brain stem, affecting in particular the efferent pathways. On the other hand, the degenerative changes in the trapezoid body and in the attached nuclei were rather mild, thereby suggesting that these were still functioning; this is commensurate with the clinical findings in the patient during intervals when cerebral oedema was absent and the patient's hearing on both ears was normal. The latter is in accord with findings obtained by *Mettler et al.* (1934) in experiments in which they destroyed one hearing centre together with the ipsilateral portion of the brain stem: the trapezoid body remained intact (fig. 3 corresponding to fig. 18 in treatise A).

Throughout the two postoperational periods in which the cerebral oedema was manifest, also *the left hemisphere* was partly out of action. In other words, both hearing centres were compromised: consequently the patient's hearing failed, in particular his hearing of sounds in the high-frequency range (fig. 4 corresponding to fig. 19 in treatise A).

The patient died of acute pulmonary embolism after the second surgical intervention, at a time when the cerebral oedema was manifest and the hearing loss clinically reminded of that observed by *Johansen* in a series of normal, 75 year-old patients (*Johansen* 1943): considered from a patho-anatomical point of view the brain which was fixed *in situ* was in a condition like that observed at the audiometric examination when audition of pure tones had been lost because an acute, diffuse, cerebral oedema had been added to the chronic pathological lesions: consequently the left hearing centre had been blocked: the right hearing centre had been destroyed at an earlier stage (fig. 4 corresponding to fig. 19 in treatise A).

It is worth noticing that the acute changes of the brain stem were less marked than those of the cerebral hemisphere and that the left temporal bone remained intact.

II Acute lesions which are presumed to impair functions in the areas concerned

1 Oedema and degeneration involving the left cortical hearing centre
2 Severe, acute degeneration of the white substance in the left temporal lobe

III Lesions localized to other pathways and nuclei in the brain stem were small only and may not have exerted any clinically demonstrable influence on the patient s hearing It should be particulary stressed that the chronic and acute lesions were negligible in the right and left ventral and dorsal cochlear nuclei in the trapezoid body in the left inferior colliculus and in the medial geniculate body on either side

Discussion and Conclusion

Mettler et al (1934) demonstrated in experiments on dogs that extirpation of th cortical hearing centre in one hemisphere did not affect the hearing essentially whereas destruction involving both hemispheres would be responsible for a hearing loss of 70–75 decibel at a frequency of 1000 cycles per second (c p.s.) Further more this author observed that the acoustic value of crossed and non-crossed pathways in the brain stem was identical since one aspect of the brain stem together with the ipsilateral cerebral hemisphere might be injured without affecting the hearing capacity if only the trapezoid body was preserved

In previous studies by for instance *Nylén* (1939) *Lemoyne* (1944) *Bocca et al* (1955) *Carmichael et al* (1956) *Goldstein* (1961) and *Maspétiol et al* (1961) human audition was found to remain uninfluenced by lesions involving only one cerebral hemisphere The entire tone range may remain audible even after hemispherectomy (*Dandy* 1937)

Henschen (1920) did not observe loss of hearing in any of his 14 patients with lesions involving both hemispheres but an intact temporal lobe on one side

On the other hand, some reports have been concerned with bilateral lesions localized to the transverse gyri or the white substance in both cerebral hemispheres in which cases the hearing capacity apparently was extinct (*Strohmayer* 1901 *Campbell* 1905 *Henschen* 1916–1918 1920 *Fraser & Nelson* 1928)

As regards the patient discussed by *Fraser & Nelson* both cochleae had been inspected simultaneously The right cochlea was found to be normal while sequelae after a severe inflammation of the middle ear on the other side were in evidence

Special interest is attached to the reports on patients with normal hearing who had experienced previous episodes of cerebral apoplexy but lost their hearing later after repeated vascular episodes Five case histories of this type are available some of the patients were young, others were elderly individuals. The apoplectic episodes were attributable to embolism following endocarditis or mitral stenosis, to thrombosis in connection with cerebral arteriosclerosis or in one case to hae morrhages in cerebral hydatid cysts All of these patients survived for a couple of weeks after the vascular episode which had been responsible for their hearing

loss. In the cases described by *Sérieux & Mignot* (1901) and by *Bramwell* (1927), post-mortem inspection of the brains exposed extensive destructive changes in the temporal lobes on either side. The patient described by *Mott* (1907) presented severe lesions localized to all transverse gyri including the white substance on one side, while the pathological changes in the other hemisphere exclusively were localized to the cortex in the hearing centre. *Misch* (1928) observed that the lesion in his patient was localized only to the anteromedian part of the superior temporal gyrus of one hemisphere while the transverse gyri on the other side were totally destroyed. Finally the extensive pathological, bilateral changes in the internal capsules involved also the acoustic radiation. In contrast, the cerebral cortex was found to remain normal in the deaf patient described by *Clark & Russell* (1938).

The above cited studies seem to indicate that the hearing capacity in man remains uninfluenced by unilateral hemispheric lesions whereas it will be extinct in patients in whom destructions involve the acoustic areas in both cerebral hemispheres. In the patient here discussed, the destruction of the right hearing centre may have been due to the severe oedema previously provoked by the tumour which involved the right cerebral hemisphere. Furthermore, ingrowth of the tumour into the right internal capsule may have been responsible for the severe right-sided, chronic degeneration of the brain stem, affecting in particular the efferent pathways. On the other hand, the degenerative changes in the trapezoid body and in the attached nuclei were rather mild, thereby suggesting that these were still functioning; this is commensurate with the clinical findings in the patient during intervals when cerebral oedema was absent and the patient's hearing on both ears was normal. The latter is in accord with findings obtained by *Mettler et al.* (1934) in experiments in which they destroyed one hearing centre together with the ipsilateral portion of the brain stem: the trapezoid body remained intact (fig. 3 corresponding to fig. 18 in treatise A).

Throughout the two postoperational periods in which the cerebral oedema was manifest, *also the left hemisphere* was partly out of action. In other words, both hearing centres were compromised, consequently the patient's hearing failed, in particular his hearing of sounds in the high-frequency range (fig. 4 corresponding to fig. 19 in treatise A).

The patient died of acute pulmonary embolism after the second surgical intervention, at a time when the cerebral oedema was manifest and the hearing loss clinically reminded of that observed by *Johansen* in a series of normal, 75-year-old patients (*Johansen*, 1943) considered from a patho-anatomical point of view: the brain which was fixed *in situ* was in a condition like that observed at the audiometric examination when audition of pure tones had been lost because an acute, diffuse, cerebral oedema had been added to the chronic pathological lesions; consequently the left hearing centre had been blocked, the right hearing centre had been destroyed at an earlier stage (fig. 4 corresponding to fig. 19 in treatise A).

It is worth noticing that the acute changes of the brain stem were less marked than those of the cerebral hemisphere and that the left temporal bone remained intact.

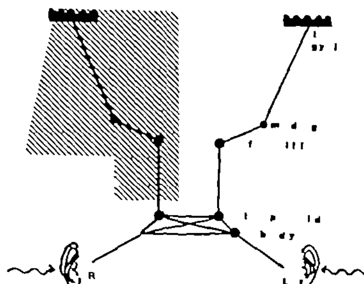


Fig. 3. The patient discussed in chapter II. Sketchy representation of localizations of the chronic pathological processes in relation to the cerebral auditory pathways and centres, hatched areas representing the pathological processes.

It seems reasonable to conclude on the basis of these clinical and pathological facts that the patient's loss of hearing, particularly his failing perception of tones in the high-frequency range, to a lesser degree of those in the low-frequency range (similar to features encountered in 75-year-old patients with presbycousis) may have been provoked by the recurring oedemas in the cerebral hemispheres. In other words, the hearing capacity is seen to fluctuate parallel with pathologically changing conditions in the brain.

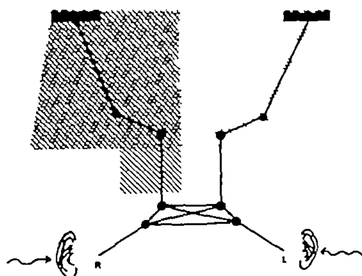


Fig. 4. The patient discussed in chapter II. Sketchy representation of localizations of the chronic (hatched area) and acute (dotted area) pathological processes in relation to the cerebral auditory pathways and centres.

CHAPTER III

Previous Studies of Senile Changes Involving the Peripheral Auditory Organ and the Central Auditory Pathways

The clinical findings in cases of perceptive hearing loss in old age are generally known, but the patho-anatomical factors responsible for the impaired hearing are much discussed, this applies to localization of lesions in and round about the peripheral auditory organ and the central auditory pathways as well as to the aetiology of these lesions.

Numerous studies are available in which audiometric findings have been collated with those obtained in patho-anatomical studies of the labyrinth.

Studies concerning the state of the central auditory pathways and centres in patients whose hearing is impaired due to age, however are less numerous.

The literature on these topics is comprehensive. The author has tried to select publications with relevance to the individual structures, fully realizing that there may be some overlapping.

A Changes involving the epithelial cochlear elements

Descriptions of the following lesions are on record. Flattening and degeneration of the organ of Corti, reduced number or complete absence, of hair cells and flattening of the supporting cells Occasionally the tectorial membrane may be thin and be incorporated into the formation of synechia Reissner's membrane has often been seen to adhere downwards over the organ of Corti (e.g. *Saxén* 1952 *Jørgensen* 1961)

According to the selected publications, the lesions may be attributable to (1) Angiosclerosis involving the internal ear (2) failing nutrition of the organ of Corti via the endolymph (3) atrophy due to old age (4) secondary atrophy owing to lesions of the spiral ganglion of the cochlea, and (5) changes to occur at terminal stages or after death

re (1) The incidence as well as the spread of angiosclerotic lesions increase parallel with age this is particularly true of lesions at the site of the vascular stria. According to *Fabinyi* (1931), *Crowe et al* (1934) *Schuknecht* (1955) and *Jørgensen* (1961), they occur uniformly throughout all coils. A parallelism between degrees of vascular changes and degeneration of the organ of Corti is not demonstrable (*Crowe et al.*, 1934 *Saxén* 1952 *Schuknecht* 1955 *Jørgensen* 1961). According to *Covell and Rogers* (1957), stria vessels of normal appearance may be encountered in areas displaying complete atrophy of the organ of Corti.

re (2) According to modern physiological and histochemical studies the organ of Corti is supplied through the endolymph secreted from the vascular stria, cf *Jørgensen* (1962) It is open to discussion, however whether a reduced secretion of the endolymph due to pathological processes in the vascular stria, may be responsible for the deafness to develop in old age since, as already mentioned, there is no correlation between the pathological processes in the vascular stria and those in the organ of Corti

re (3) Schuknecht (1955) declared that senile atrophy of the cochlea was the otological manifestation of processes due to age which are in evidence in all tissues throughout the body Such atrophy has been found to begin in the basal cochlear coil and to include all structures of the middle scale, for instance the afferent and efferent fibres

re (4) The epithelial changes may be secondary to the disappearance and degeneration of nerve cells in the spiral ganglion of the cochlea. This postulation is corroborated by the fact that epithelial changes rarely are encountered in cochlear areas where ganglion cells are intact (*Saxén* 1952 *Covell and Rogers* 1957) *Schuknecht* (1953) managed to destroy the neural elements in cats, escaping a development of secondary lesions of the organ of Corti.

re (5) Finally the histologically demonstrable changes in epithelial elements may have been provoked by such diseases as were responsible for the death of the patients or by changes to develop at terminal stages also the fixation time and fixation techniques may play some role (*Lange* 1937)

In addition to the lesions localized to the middle scale, *Mayer* (1919) observed a thickening of the basilar membrane at which site calcareous deposits were in evidence mainly in the basal coil Such lesions however have later been seen also in patients whose hearing was normal (*Crowe et al* 1934)

According to *Saxén* (1952) and *Fleischer* (1956), the above mentioned histopathological changes are not constant findings in the epithelial elements of the cochlea in elderly patients exclusively the same feature has actually been encountered even in 7 year-old patients by *Jørgensen* (1961)

Hence if these histopathological changes, which all were demonstrable by histological routine section and staining technique, were collated with those observed by audiometric examination of patients with presbycousis, it seemed highly improbable that the demonstrated pathological changes had been exclusively responsible for the loss of hearing. The reason may be that the clinical procedures the histological and the biochemical techniques were not sufficiently delicate to disclose such correlation. Accordingly a few studies in which these more advanced techniques were used shall be cited

Using the monaural balance test which according to *Pestalozza and Shore* (1955) represents a standard of the functioning capacity of hair cells these authors found values to be within the normal range in one half of all individuals in their series of patients with presbycousis.

Ruben (1963) found the cochlear microphonic potential (C M) to be within normal range in the basal coil in an elderly patient whose deafness to tones in the high frequency range was of the classic presbycousis type According to the

investigation, this indicates that functions of hair cells were fair at cochlear sites where high-frequency tones are perceived.

In a study of cochleae from elderly patients, *Bredberg* (1968) demonstrated by phase contrast microscopy of cochleae perfused with osmic acid that the disappearance of hair cells might be of different importance in the individual coils. At apical sites there tones in the frequency range 250 cycles per second are presumed to be perceived, the loss of hearing of tones in this range did not exceed 40 decibel even though up to 50 / or 75 / of the external hair cells had disappeared. Conversely in areas where tones in the range 8000 cycles per second are presumed to be perceived, a relatively smaller loss of external hair cells might result in a hearing impairment of a more severe degree. The author failed to demonstrate, however whether the *pro rata* loss of *internal* hair cells might be correlated with the loss of hearing of tones in the high frequency range.

Such lacking correlation between degrees of degenerative changes in the organ of Corti and the functioning capacity of the latter has been observed also in guinea pigs by *Schnieder and Janzer* (1969) These authors induced lesions of hair cells by means of the socalled "white noise As a standard of the degenerative changes, the lactose concentration in the perilymph was analysed and the results collated with the measured cochlear microphone potential were determined. Thus, the authors were able to demonstrate that even a considerable loss and degeneration of hair cells in the frequency range 4000 cycles per second did not reduce the cochlear microphone potential in the area of the basal cochlear coil.

On the basis of the above cited studies, it may be reasonable to presume that the degenerative changes in the epithelial elements of the cochlea hardly can be exclusively responsible for the hearing loss applying to tones in the high-frequency range, a loss which otherwise is typical in cases of presbycousis.

B Changes involving the vessels of the temporal bone and the vessels of the circle of Willis

Vascular changes in the membraneous portion of the cochlea are hardly contributory to a development of presbycousis. As previously mentioned, any parallelism between degrees of angiosclerosis in the vascular stria and degeneration of the organ of Corti is not in evidence and the same applies to vessels in the modiolus Besides, the pathological changes involving the cochlear vessels were not directly correlated with the degenerative lesions in the spiral ganglion of the cochlea (*Crowe et al.* 1934 *Saxén* 1952, *Schuknecht* 1955 *Covell and Rogers* 1957).

As regards the vascular changes involving the osseous capsule of the labyrinth, whether or not of any importance, *Gussen* (1968, 1969) ascertained, on the basis of conventionally stained celloidin sections, that the vascular supply apparently remained satisfactory even in very old subjects in fact, it did not deviate much from that observed in young subjects. In patients with presenile arteriosclerosis, however a development of thrombi in these vessels seemed to be more common (*Gussen* 1969).

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It is still open to discussion whether vascular changes involving the peripheral auditory organ may be correlated with changes in the cerebral vessels and, likewise, whether changes in the circle of Willis may be correlated with those in vessels running through the internal auditory canal

Saxén (1952) observed angiosclerosis in vessels of the internal ear although coincident lesions of vessels in the internal auditory canal and those at the base of the brain were absent in renal vessels, however arteriolosclerosis was in evidence. On the other hand *Jørgensen* (1961) declared that there might be a certain correlation between vascular changes in the vascular stria and those in the cerebral vessels, in particular in those at the base of the brain On the basis of findings in a series of old patients, *Ishii* (1967) concluded that pathological changes in the basilar arteries, including the anterior inferior cerebellar arteries and those in the internal auditory canals, need not be correlated with lesions affecting the various structures of the internal ear

In a study of a series of senile patients, *Fabinyi* (1931) compared the audiometric findings with the pathological processes in the large cerebral arteries. There was apparently some correlation between loss of hearing of tones in the high-frequency range and degrees of cerebral arteriosclerosis, but the relation between the loss of hearing of tones in the high frequency range and changes in internal auditory canal vessels was less clear-cut.

C Histopathological changes involving the spiral ganglion of the cochlea

Disappearance and degeneration of ganglion cells in the spiral ganglion of the cochlea are mainly demonstrable in the basal coil and represent the patho-anatomical process most constantly encountered in the labyrinth of elderly patients (*Crowe et al* 1934 *Saxén* 1952 *Schuknecht* 1955 and *Jørgensen* 1961) According to *Fleischer* (1956) these lesions were the only ones to intensify parallel with advancing years consequently he suggested that the neural changes might be solely responsible for the development of presbycousis

Fabinyi (1931) and *Crowe et al* (1934) have declared that degrees of changes in the ganglion cells of the basal coil might be correlated, though not absolutely with the degrees of hearing loss applying to tones in the high frequency range In patients whose hearing was severely impaired, *Crowe et al* (1934) and *Saxén* (1952) observed, however that pathological processes involving the spiral ganglion might occasionally be of moderate degree

In patients whose hearing is normal and who perceive tones in the high- as well as the low-frequency range, the percentage of damaged ganglion cells in the basal coil has been differently calculated by the individual authors for instance, it has been found to range at 50 (*Crowe et al* 1934) at 75 (*Schuknecht* 1955), even up to 80 (*Citron et al.* 1963)

In a series of patients with presbycousis, *Saxén* (1952) observed that the percentage of degenerated nerve cells in the basal coil often might range below 50 while the percentage of ganglion cells in the middle and apical coil generally was

within normal range, even though perception of tones in the low-frequency range was found to vary greatly from patient to patient.

Obviously a loss of hearing need not be correlated with a degeneration of neural elements, whether in basal, middle, or apical coils. Hence it seems highly improbable if patho-anatomical lesions in the spiral ganglion were solely responsible for a development of presbycusis.

"The reason why the atrophic change selects the basal end is as great a mystery to me as the process of ageing itself" (*Schuknecht* 1955)

Evidently such changes in the spiral ganglion need not be secondary to a degeneration of the efferent pathways in the cochlea and, in fact, atrophic ganglion cells were not in evidence several weeks after bisection of the olivo-cochlear bundle (*Rasmussen*, 1953).

D. *Degeneration of the acoustic nerve throughout the tractus spiralis foraminosus and the internal auditory canal*

Sërcer and Krmpotić (1958) observed some hyperosteotic lesions at the site of tractus spiralis foraminosus, mainly involving the area where nerve fibres emerge from the basal coil. These findings may explain to some extent why perception of high tones may be impaired in old age, although other authors have failed to confirm the phenomenon.

According to *Crowe et al.* (1934) the patho-anatomical lesions involving the cochlear nerve throughout the internal auditory canal may be of a degree more pronounced than that of the degenerative changes in the organ of Corti.

It remains obscure, however, whether such changes may be responsible for the loss of hearing in old age. *Neff* (1947) found that tones in the high-frequency range were imperceptible to experimental animals if more than 50 % of all fibres in the cochlear nerve had been bisected, in contrast, *Schuknecht and Woellner* (1953) who destroyed 75 % of this nerve in cats, avoided injuring the hearing.

In patients with acoustic neurinomas, severe degeneration of the cochlear nerve need not be associated with impaired perception of pure tones (*Schuknecht and Woellner* 1955 *Jerger* 1960 *Citron et al.*, 1963 *House* 1968)

It does not appear from the above cited studies, however whether the histopathologically demonstrable lesions were localized to the peripheral (Schwann's) or the central (glial) part of the cochlear nerve.

Thus, it can be established that many investigators have pointed to the fact that the pathological changes of structures in the temporal bone are not exclusively responsible for a loss of hearing late in life.

E. *Pathological processes involving the cerebral auditory pathways and centres*

Reports concerning the status of the auditory areas in the brains of patients with presbycusis are scarce.

According to *Scheidegger* (1963), several types of diffuse, degenerative lesions

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CHAPTER IV

Analysis of the Pathological Processes Involving the Peripheral Auditory Organ and Central Pathways in Twelve Senile Patients Whose Loss of Perceptive Hearing was Verified

As mentioned in chapter III, numerous authors have discussed the patho-anatomical processes involving the cochlea as well as the central auditory pathways, processes which may have been responsible for the loss of hearing in old age the authors concerned have correlated the loss of hearing with pathological processes localized exclusively to cochlear structures or to sites within the central auditory pathways and centres.

In a further attempt to define the patho-anatomical factors responsible for the loss of hearing in old age and to localize the origin, or origins, of such loss, a parallel has been drawn between the findings obtained by audiometry and the pathological lesions of the central auditory pathways and lesions of the temporal bone structures As far as the author is aware, this type of study has not yet been performed

According to patho-anatomical criteria, the 12 patients comprised in the series can be classified into four groups of 8 2, 1 an 1 patients. The patients concerned have previously been discussed in treatise B of which an abstract follows

Group I 8 patients

The past medical histories of these eight patients were identical which applies also to the audiological and patho-anatomical findings, though individual variations might be encountered.

Table 1 represents a survey of findings by audiometry incidence of intercurrent diseases, causes of death, and autopsy findings in organs from the eight patients, the series comprised four men and four women at ages above 80 years except one who was only 66 years old

The blood pressure was normal according to age in all patients except in the patient classified into group III.

The past audiological histories contained no data which might explain why these patients had lost hearing indeed patients nos. 3 and 5 had experienced left sided otitis media while the remaining six patients had perceptive deafness, presenting symmetrical hearing curves (fig 5 corresponding to figs. 15–22 in treatise B)

The average value of intelligibility thresholds in the ranges 250 500, and 1000 cycles per second, i.e. the low-frequency ranges, varied from 10 decibel to 60 decibel As regards the high-frequency range, audition was severely impaired in all

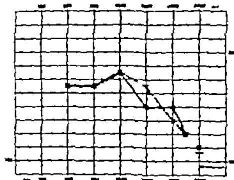
might occur in brains of presenile or senile patients, for instance, cerebral arteriosclerosis, senile atrophy Alzheimer's syndrome, Pick's disease, and the socalled presenile spongious cerebral atrophy There is reason to suppose that similar lesions may be encountered also in the cerebral auditory pathways and centres

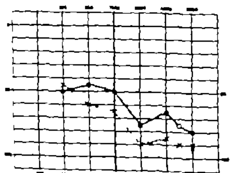
On the basis of findings in studies of the pathological processes involving the peripheral auditory organ, *Sporleder* (1899) *Crowe et al* (1934) *Saxén* (1952) *Schuknecht* (1955) and *Ishii* (1967) failed to provide a sufficiently reliable explanation of the auditory lesions in patients with presbycousis consequently they postulated that degenerative lesions in old patients also might involve the more centrally localized areas This postulation was confirmed by *Kirikae et al* (1964) who in brains from 11 senile patients, found degeneration of ganglion cells in the ventral cochlear nucleus, in the superior olivary nucleus, in the inferior colliculus, and in the medial geniculate body

The present author has not been able to procure studies including detailed data concerning the correlation of the hearing capacity in man and the cortical processes, if any involving the auditory centres in the cerebral hemispheres.

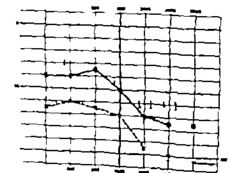
Finally reports concerning the histopathologically demonstrable processes in the temporal bones and brains of senile patients with presbycousis are not available


No 1


No 2.


No 3


No 4


No 5


No 6

Table I Audiological Examination

Group		Age	Sex	B P	Low-frequency mild < 40 medium > 40	Highest frequency severe > 60	Audiology prior to death	Cause of death	Other diseases
I	(1)	86	♂	160/80	severe	extinct	14 months	Broncho-pneumonia	Arteriosclerosis
	(2)	82	♀	175/70	medium	extinct	60 days	Pulmanary embolism	Arteriosclerosis
	(3)	91	♀	170/80	medium	severe	24 days	Coronary occlusion	Arteriosclerosis
	(4)	80	♀	130/90	medium	severe	6 years	Coronary occlusion	Arteriosclerosis and leukaemia
	(5)	89	♂	145/100	medium	extinct	3½ years	Cerebral apoplexy	Arteriosclerosis
	(6)	83	♀	110/80	mild	severe	8 days	Pulmanary embolism	Arteriosclerosis and tuberculosis
	(7)	66	♂	105/60	mild	severe	2½ years	Carcinoma of the gall bladder	Arteriosclerosis
	(8)	88	♂	180/90	medium	extinct	18 days	Pulmanary embolism	Arteriosclerosis and cancer of the caecum
II	(9)	80	♂	160/100	mild	severe	12 days	Croupous pneumonia	Arteriosclerosis
	(10)	79	♂	140/80	m ld	extinct	1 year	Coronary thrombosis	Arteriosclerosis
III	(11)	60	♂	40/130	mild	severe	2 years	Cerebral apoplexy	Arteriosclerosis
IV	(12)	69	[illegible]	145/85	m ld/ extinct	severe/ extinct	6 years	Acute Pyelonephritis	Arteriosclerosis

Patients discussed n chapter IV
Pathological findings in temporal bones.

Table 2 Temporal Bones

Group	Organ of Corti, comments	Vessels in the internal auditory canal, including the intraneural vessels	Ganglion cells in the basal cochlear coil	The auditory nerve inside the internal auditory canal: Peripheral part	Glial part
I	Deformed and flattened	Thickening of walls, luminal stenosis	+/+	+/+	++/++
	Deformed and flattened	Thickening of walls, luminal stenosis	+/+	++/++	+++/+++
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	absent/++	absent/+++
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	+/+	+++/+++
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	++/absent	++/absent
	Deformed and flattened	Thickening of walls, luminal stenosis	normal/normal	+/+	bsent/ bsent
	Left sided hydrops	Thickening of walls, luminal stenosis	+/+	+/absent	++/absent
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	++/++	absent/absent
II	Deformed and flattened	Thickening of walls, luminal stenosis	+/absent	++/ bsent	+++/absent
	Deformed and flattened	Slight thickening of walls, luminal stenosis	+++/+++	+/+	++/++
III	Normal throughout	Thickening of walls, luminal stenosis	normal/normal	sporadic demyelinisation	severe demyelinisation
IV	Left-sided hydrops	Almost normal vessel	+++/absent	+++/only few myelin sheats + axons	+++/++++

Patients discussed in chapter IV
Pathological findings in temporal bones.

patients, occasionally the walls had thickened moderately but stenosis of the lumens was a rare occurrence On the other hand, the walls of the vessels in the internal auditory canal as well as the walls of intraneural vessels had thickened in some cases and lumens might be constricted it applied to all patients that the vascular changes were more pronounced than those in the vascular stria and the modiolus The intraneural changes were most marked in the glial part of the nerves

The number of ganglion cells was normal, or faintly reduced, in the apical and the middle coil of the spiral ganglion degenerative changes if any were neglig'ble In the basal coil, however symmetrical disappearance and degeneration of cells in the spiral ganglion ranged from slight to moderate

According to patho-anatomical criteria, the acoustic nerve in the internal audi-

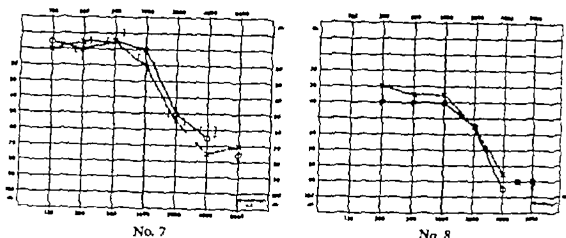


Fig 5 Audiograms from the patients in group I (nos. 1–8, table 1).

patients Discrimination losses in five patients were in the range moderate to severe

Vestibular irrigation, using water at about 20–30 C, gave normal and uniform reactions in all patients

Four patients died of pulmonary diseases, two died of coronary sclerosis, one died after an apoplectic attack, and one died of metastases to the liver from a carcinoma of the gall bladder

Autopsy inspection of organs disclosed severe arteriosclerotic lesions in all cases.

The pathological findings in the temporal bones were of identical nature in all patients although the intensity of the degenerative lesions might vary individually (table 2)

The middle ear was of normal appearance in all but two patients, nos. 3 and 5 in whom the left ossicles were sites of severe osteitic lesions adherances through the middle ear were broad and the tympanic membrane had thickened.

In another patient, no 8 a cholesteatoma, not involving the ossicles, was in evidence, i e a "cholesteatoma in situ

All structures in the middle scale i.e the vascular stria, the sulcus cells, and the organ of Corti, were found to be deformed and flattened Changes varied from coil to coil from section to section and from the right to the left temporal bone in one and the same patient. Especially the appearance of the organ of Corti varied in most sections it was hardly recognizable, while structures appeared rather well preserved in other sections from the apical coil, the middle coil and the basal coil The tectorial membrane was displaced in relation to the organ of Corti while Reissner's membrane in many sections seemed to adhere downwards over the organ Lesions in the organ of Corti appeared to be uniformly dispersed throughout all coils

The basilar membrane had not thickened appreciably in any of the patients, particularly not at the site of the basal coil any calcareous deposits were not observed.

Vessels in the vascular stria and in the modiolus appeared to be normal in all

Table 2 Temporal Bones

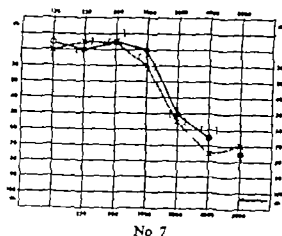
[illegible]	Organ of Corti, [illegible]	[illegible] in the internal auditory canal, including the intraneural vessels	Ganglion cells in the basal cochlear coil	The auditory nerve inside the internal auditory canal: Peripheral part	Glial part
	Deformed and flattened	Thickening of walls, luminal stenosis	+/+	+/+	++ ++
	Deformed and flattened	Thickening of walls, luminal stenosis	+/+	++/++	+++/+++
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	absent/++	absent/+++
I	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	+/+	+++/+++
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	++ bsent	++/absent
	Deformed and flattened	Thickening of walls, luminal stenosis	normal/normal	+/+	absent/absent
	Left sided hydrops	Thickening of walls, luminal stenosis	+/+	+/absent	++/absent
	Deformed and flattened	Thickening of walls, luminal stenosis	++/++	++/++	absent/absent
II	Deformed and flattened	Thickening of walls, luminal stenosis	+/absent	++/absent	+++/absent
	Deformed and flattened	Slight thickening of walls, luminal stenosis	+++/+++	+/+	++/++
II	Normal throughout	Thickening of walls, luminal stenosis	normal/rormal	sporadic demyelinization	severe demyelinization
V	Left-sided hydrops	Almost normal vessels	+++/absent	+++/only few myelin sheats + axons	+++/++++

Patients discussed in chapter IV
Pathological findings in temporal bones

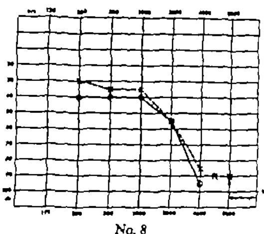
patients, occasionally the walls had thickened moderately but stenosis of the lumens was a rare occurrence. On the other hand, the walls of the vessels in the internal auditory canal as well as the walls of intraneural vessels had thickened in some cases and lumens might be constricted, it applied to all patients that the vascular changes were more pronounced than those in the vascular stria and the modiolus The intraneural changes were most marked in the glial part of the nerves.

The number of ganglion cells was normal, or faintly reduced, in the apical and the middle coil of the spiral ganglion degenerative changes, if any were negligible. In the basal coil, however symmetrical disappearance and degeneration of cells in the spiral ganglion ranged from slight to moderate.

According to patho-anatomical criteria, the acoustic nerve in the internal audi-



No 7



No. 8

Fig 5 Audiograms from the patients in group I (nos. 1–8 table 1).

patients Discrimination losses in five patients were in the range moderate to severe

Vestibular irrigation, using water at about 20–30 C, gave normal and uniform reactions in all patients

Four patients died of pulmonary diseases, two died of coronary sclerosis, one died after an apoplectic attack, and one died of metastases to the liver from a carcinoma of the gall bladder

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The pathological findings in the temporal bones were of identical nature in all patients although the intensity of the degenerative lesions might vary individually (table 2)

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In another patient, no 8 a cholesteatoma not involving the ossicles was in evidence, i e. a "cholesteatoma *in situ*

All structures in the middle scale, i.e the vascular stria, the sulcus cells, and the organ of Corti were found to be deformed and flattened. Changes varied from coil to coil from section to section and from the right to the left temporal bone in one and the same patient. Especially the appearance of the organ of Corti varied in most sections it was hardly recognizable while structures appeared rather well preserved in other sections from the apical coil, the middle coil, and the basal coil The tectorial membrane was displaced in relation to the organ of Corti while Reissner's membrane in many sections seemed to adhere downwards over the organ *Lesions in the organ of Corti appeared to be uniformly dispersed throughout all coils.*

The basilar membrane had not thickened appreciably in any of the patients particularly not at the site of the basal coil any calcareous deposits were not observed

Vessels in the vascular stria and in the modiolus appeared to be normal in all

Additional sections of brains disclosed diffuse pathological processes similar to those observed in the auditory pathways.

Group II 2 patients

The past medical histories of the two patients concerned were similar to those of patients in group I and the audiometric findings in patients in the two groups were identical (cf fig 6, corresponding to figs. 24–25 in treatise B)

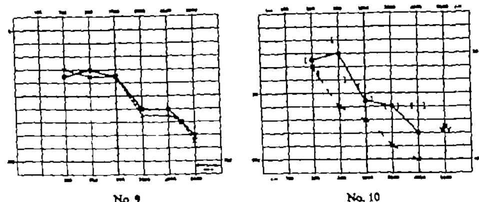


Fig 6 Audiogram from the patients in group II. (nos 9–10, table 1).

In one patient (a 79-year-old man, cf. table 1) the impaired hearing may in part have been due to the noise produced by his trade since he throughout 56 years had been working as a cooper

One of these patients died of croupous pneumonia, the other of coronary thrombosis.

Findings obtained by histological examination of the middle ear the internal ear and the acoustic nerve were identical with the degenerative changes observed in patients in group I, table 2.

Both brains were sites of degenerative lesions like those seen in brains from patients in group I but atherosclerosis was not in evidence. The walls of arterioles had thickened, being of granular structure as otherwise seen in cases of senile atrophy

Thus, findings in the ten patients in groups I and II included, symmetrical loss of perceptive hearing, pathological processes involving the temporal bones, in particular the basal cochlear coil, and degeneration of the central auditory pathways and nuclei

Group III 1 patient

Group III comprises only one patient whose past medical history deviates from that of the aforementioned patients in that his loss of hearing had meant a handicap since he was about 58 years old. In addition, his blood pressure, systolic as well as diastolic, was elevated.

tory canal can be divided into two parts, one peripheral containing Schwann s cells and one central, glial part. In the peripheral part, disappearance and degeneration of myelin sheaths and axis cylinders would be of about the same order as in the basal coil of the spiral ganglion In the glial part, disappearance of myelin sheaths and axis cylinders was of about the same order while degeneration was by far more intense Numerous amyloid bodies were demonstrable at the junction between the two parts

It should be noted, however that Scarpa s vestibular ganglion as well as the vestibular nerve were sites of only few if any patho-anatomical lesions in all patients

At gross inspection of the central nervous system all brains were found to be diffusely atrophic infarctions were demonstrable in a few of the brains The leptomeninges were diffusely blurred.

Vessels in the circle of Willis were moderately to severely atherosclerotic Dilatation of the ventricular system was of varying degrees

Findings obtained by microscopy of the central auditory pathways included slight to moderate disappearance of cells in the glial part of the acoustic nerve and severe degenerative changes of myelin sheaths and axis cylinders The walls of intraneural vessels had thickened

Disappearance and degeneration of cells in the ventral and dorsal cochlear nuclei were symmetrical, being most marked in the latter Exactly the same type of lesions were demonstrable in the superior olivary nucleus, in the inferior colliculus, and in the med al geniculate body

Myelin sheaths and axis cylinders in the auditory pathways throughout the brain were swollen and unevenly calibrated

The white matter in the cortical auditory centres displayed varying degrees of thinning out with degeneration of myelin sheaths and axis cylinders

Focal and diffuse disappearance and degeneration of the cortical ganglion cells were in evidence in addition cortical malacias were manifest in three patients in one of these (no 1 in group I table 1) the left transverse gyri were involved in another (no 2 in group I table 1) both transverse gyri were involved, and in one patient (no 5 in group I table 1) the right transverse gyri were involved

Vessels in the cerebrum the brain stem and in the leptomeninges were severely damaged. In addition to the atherosclerotic lesions observed by gross inspection, the arteries and veins of intermediate size were sites of perivascular fibrosis the connective tissue in the walls had amplified The walls of arterioles were of a thickened homogenous appearance and the lumens were constricted, occasionally they might be totally occluded. Fibrillary thickening of the capillaries was in evidence

The pathological processes involving the cortex in the transverse gyri (the central auditory centres) were apparently not more severe than those in the auditory nuclei in the brain stem whereas processes involving the glial portion of the acoustic nerve and the white matter in the auditory centres were more severe than those in the auditory pathways through the brain stem

The processes seemed to occur symmetrically

Additional sections of brains disclosed diffuse pathological processes similar to those observed in the auditory pathways.

Group II 2 patients

The past medical histories of the two patients concerned were similar to those of patients in group I and the audiometric findings in patients in the two groups were identical (cf. fig. 6 corresponding to figs. 24–25 in treatise B)

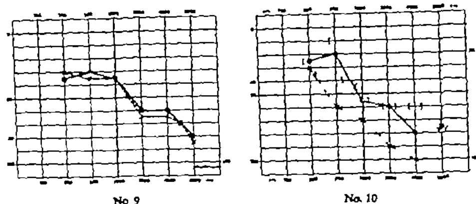


Fig 6 Audiogram from the patients in group II (nos 9–10 table 1)

In one patient (a 79-year-old man, cf. table 1), the impaired hearing may in part have been due to the noise produced by his trade since he throughout 56 years had been working as a cooper

One of these patients died of croupous pneumonia, the other of coronary thrombosis.

Findings obtained by histological examination of the middle ear the internal ear and the acoustic nerve were identical with the degenerative changes observed in patients in group I, table 2.

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Thus, findings in the ten patients in groups I and II included, symmetrical loss of perceptive hearing, pathological processes involving the temporal bones, in particular the basal cochlear coil, and degeneration of the central auditory pathways and nuclei.

Group III 1 patient

Group III comprises only one patient whose past medical history deviates from that of the aforementioned patients in that his loss of hearing had meant a handicap since he was about 58 years old. In addition, his blood pressure, systolic as well as diastolic, was elevated.

3

The patient was a 60-year-old man who previously had been in good health his hearing had been normal During the last two years prior to death he became increasingly demented and complained of uncharacteristic vertigo and impaired hearing. One year before death, a haemorrhage in the right hemisphere occurred Audiometry revealed symmetrical loss of perceptive hearing the loss of hearing was of the presbycousis type and of a severity common in 75 year-old individuals, according to *Johansen*s findings in a series of normal subjects (*Johansen* 1943) cf fig. 7 corresponding to fig 26 in treatise B

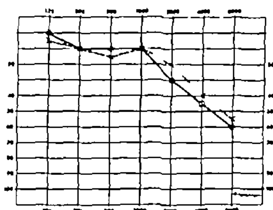


Fig 7 Audiogram from the patient in group III (no 11 table I).

In addition, the loss of discrimination ranged at 67 % determined by free-field speech audiometry

The patient died one year later in continuation of recurring cerebral vascular episodes.

It should be emphasized that the brain was fixed *in situ* about 10 minutes after death had occurred.

Autopsy inspection of organs revealed severe generalized atherosclerosis.

Microscopy of the temporal bones (table 2) The organ of Corti was of normal appearance. The walls of the cochlear vessels were slightly thickened The cochlear spiral ganglion was normal

Axis cylinders in the peripheral part of the acoustic nerve had not disappeared but sporadic demyelination was in evidence intensifying towards the glial part.

Vessels in the internal auditory canal and the acoustic nerves were markedly arteriosclerotic

All lesions of the temporal bones were symmetrical.

At gross inspection and by microscopy of the brain, the right hemisphere was found to be a site of a massive fresh haemorrhage and atrocious atherosclerosis In the glial part of the acoustic nerve, demyelination was sporadic intensifying towards the cerebrum where it was almost generalized. The preserved structures in the auditory pathways and centres were sites of histologically demonstrable lesions similar to those observed in patients in group I

Group IV 1 patient

Also group IV comprises only one patient in whom findings deviated from those observed in patients in the other groups in that audition in the left ear was extinct. Furthermore, the patient was a chronic alcoholist.

The patient was a 69 year-old man. As far as he was able to remember bearing with his left ear had always been poor although he did not know why Since childhood, hearing with his right ear had been fluctuating on account of periodic episodes of otitis media.

Audiometry performed six years prior to his death had disclosed that audition in his left ear was extinct, audition in the right ear could not be reliably determined (cf fig. 8 corresponding to fig. 29 in treatise B) The patient being very shy it proved impossible to decide whether the right-sided loss of hearing was of the sound-conduction type or of the perception type. Also speech audiometry proved a failure

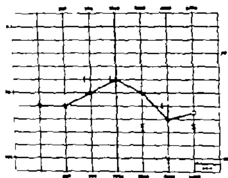


Fig. 8 Audiogram from the patient in group IV (no. 12, table 1)

The patient died when he was 69 years old, the cause of death being postoperative complications after prostatectomy

Autopsy inspection of organs disclosed acute pyelonephritis. Arteriosclerotic changes, if any were very mild

By microscopy of the right temporal bone, the middle ear and the mastoid process were found to be sites of chronic, inflammatory lesions. The ossicular chain and the tympanic membrane were intact and adherences in the middle ear were only few Otherwise findings were similar to those observed in patients in groups I and II

Examination of the left temporal bone displayed normal conditions in the middle ear Nothing of the organ of Corti remained well-preserved. Labyrinthine hydrops, involving also the saccule, was manifest. *Cells* in the spiral ganglion had disappeared almost completely and myelin sheaths and axis cylinders were scarce in the acoustic nerve.

After fixation of the brain it weighed 1300 gram It appeared normal *to* the gross view and without signs of arteriosclerosis.

Microscopy of the brain disclosed disappearance and degeneration of axis cylinders and myelin sheaths in the glial part of the acoustic nerve On the right side the changes were moderate, disappearance of cells being almost total on the left side where also the few remaining axons had degenerated.

The auditory nuclei throughout the brain stem were sites of moderate degenerative changes and the cerebral cortex displayed mild atrophy

The most severe pathological lesions were localized to the white matter in the brain stem as well as to auditory centers in the cerebral hemispheres where disappearance of cells was marked and degeneration of myelin sheaths severe similar lesions were demonstrable also in areas other than the auditory pathways.

The most significant findings clinical as well as histological in this patient included audition in the left ear was extinct, audition in the right ear being severely impaired almost total disappearance of neurones in the left spiral ganglion, and moderate degree of disappearance and degeneration of neurones in the right spiral ganglion of the cochlea. The brain was a site of diffuse demyelinization

Discussion

A brief account is given concerning data included in the past medical histories of the 12 patients comprised in this series together with descriptions of the severity of their loss of hearing and the pathological processes observed in their temporal bones and brains

The question to arise is whether it may be possible on the basis of the obtained findings to single out such lesions of peripheral and/or central elements in the auditory pathways as may be responsible for the loss of hearing.

The most essential pathological findings in temporal bones of patients in groups I and II included

Flattening of the organ of Corti which, in most cases, may have occurred after death. Uniform rather moderate vascular changes throughout the cochlea. Slight to moderate disappearance of cells in the basal coil of the spiral ganglion together with degenerative lesions involving the peripheral part of the acoustic nerve, paralleling the changes of ganglion cells. All of the observed findings were symmetrical

The pathological processes in the central auditory pathways were also symmetrical The slight to moderate disappearance of nerve fibres and the severe degeneration of the central glial part of the acoustic nerve were more marked than the disappearance and degeneration in the peripheral Schwann part degeneration of auditory pathways through the brain stem of the cortex was obviously most marked in the white matter of the cerebral hemispheres. Furthermore, atrophy of the cerebral cortex was manifest, being particularly marked in the two patients belonging in group II

Flattening of the organ of Corti and of other structures in the middle scale was observed in 11 patients. According to previous publications, this feature need not be a constant finding in elderly patients with poor hearing the phenomenon has been observed also in subjects whose hearing was normal (Crowe et al

1934 *Saxén* 1952). Furthermore, the epithelial lesions may have occurred after the death of the patients and thus, they cannot have been responsible for their loss of hearing (*Lange* 1937 *Fleischer* 1956). The latter is corroborated by the fact that the organ of Corti was found to be normal in the patient belonging in group III as well as in the 43-year-old male patient with fluctuating audition in whom a glioblastoma developed the patient has been discussed in chapter II. In both cases, the organs were fixed within 10 minutes after death.

Loss of perception of tones in the low-frequency range varied in these patients although the ganglion cells in the apical and middle coils seemed to be normal, or only slightly degenerated, thereby excluding that this part of the hearing loss was due to cochlear changes. The same conclusion has been drawn by *Saxén* (1952) on the basis of findings in his series.

The basal coil was the site of slight to moderate disappearance of ganglion cells to a certain extent, although not completely this feature may explain why the hearing of high tones was impaired in these patients. The lesions concerned, however were not more severe that those which according to the available literature may be encountered in patients with normal hearing (*Crowe et al.* 1934 *Schuknecht* 1955 *Citron et al.*, 1963)

If the rather slight vascular changes in the cochlea actually had exerted an influence on the organ of Corti and on the degenerative processes in ganglion cells, degeneration might be expected to be uniform throughout all coils because the vessels were of uniform appearance throughout the cochlea.

To all appearances, the degenerative changes of the peripheral (Schwann) part of the acoustic nerve seemed to equal those of the ganglion cells pertaining to the basal coil These changes seemed out of proportion to the very severe changes involving the extraneural vessels within the internal auditory canal.

By way of comparison it should be noted that the vestibular nerve as well as Scarpa's ganglion were normal degeneration, if any was of a mild degree in all patients

In the central auditory pathways, degeneration was of a severe character in the glial part of the acoustic nerve and in the white matter in the brain stem as well as in the auditory centres in the cerebral hemispheres. The changes were more pronounced in the cerebral hemispheres than in the white matter of the brain stem

The pathological processes in the auditory nuclei in the cortex were a little less pronounced than those involving the axons and axis cylinders in the auditory pathways

The cerebral changes might be due either to advanced age or to impaired vascular conditions It must be admitted, however that the cortical atrophy diagnosed in patients in group II was appreciable

There is reason to believe that the above discussed pathological processes involving the central nervous system in patients in groups I and II may have compromised their audition hence, lesions involving the cerebral sections of the auditory pathway may have been responsible for the loss of hearing, in particular that applying to low tones, to a minor degree that applying to high tones.

It is rather remarkable that the cochlear structures were normal throughout in

Microscopy of the brain disclosed disappearance and degeneration of axis cylinders and myelin sheaths in the glial part of the acoustic nerve. On the right side, the changes were moderate, disappearance of cells being almost total on the left side where also the few remaining axons had degenerated.

The auditory nuclei throughout the brain stem were sites of moderate degenerative changes and the cerebral cortex displayed mild atrophy

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Flattening of the organ of Corti and of other structures in the middle scale was observed in 11 patients According to previous publications this feature need not be a constant finding in elderly patients with poor hearing the phenomenon has been observed also in subjects whose hearing was normal (*Crowe et al*

In fact, it was not possible in any of the 12 patients concerned to demonstrate a correlation between the degree of the pathological processes in the internal ear and the demonstrable loss of hearing, no matter whether the hearing loss applied to tones in the high- or low-frequency range.

The conclusion to be drawn is therefore that loss of hearing "pertaining to age" presenile loss of hearing of the presbycousis type, as well as loss of hearing displaying audiometric curves of different configurations, apparently occur as sequelae of pathological processes involving the cerebrum as well as the temporal bones.

the patient in group III while sporadic demyelinization intensifying towards the cerebrum *where it was almost generalized was in evidence in the acoustic nerve* In this case it proved rather difficult to inspect the white matter and the cerebral cortex because of the oedematous nature of these From a clinical point of view however the patient concerned was almost completely demented and hence, the pathological processes to precede the acute and fatal attack must have been of a severe degree

This patient's loss of hearing applied almost exclusively to tones in the high-frequence range and, as the cochlea was of normal appearance the hearing loss could hardly be attributable to cochlear factors it may rather have been due to changes in the acoustic nerve and in the central nervous system

Lesions involving the right cochlea and the acoustic nerve in the patient in *group IV were identical with those encountered in patients in groups I and II* It should be mentioned, however that mild chronic, inflammatory changes involving the middle ear on the right side were manifest in the former patient. The degree of the inflammatory lesions was not more severe than that otherwise seen in patients with normal hearing (*Crowe et al 1934)*

The auditory pathways in the brain stem and in the cerebral hemispheres were sites of symmetrical extremely severe pathological processes in the white matter processes were less pronounced in the nuclei and the cortex Arteriosclerosis was not in evidence It seems reasonable to conclude on the basis of these findings that the right-sided loss of hearing was due mainly to cerebral changes in this patient.

Flattening of the organ of Corti in the left ear where audition had been extinct throughout years, was more marked than that in the right ear hydrops was manifest and the spiral ganglion as well as the acoustic nerve were almost completely eliminated Since lesions in the central nervous system were symmetrical it seems reasonable to presume that the left-sided loss of hearing, in excess of the right sided loss *might be ascribable to the degenerative processes in the peripheral organ*

On the basis of the findings in these 12 patients it seems justified to conclude that pathological cochlear lesions were not solely responsible for their loss of hearing, rather the pathological processes in the brain may have played some role probably even a major role

Hearing losses observed in these 12 patients were in some cases of the presbycousis type but hearing curves of other configurations were also obtained.

For instance the hearing loss experienced by the 60-year-old patient (no 11 group III) was of the presenile type and the hearing curve obtained in that case reminded of the one seen in cases of presbycousis which, according to the available reports may be encountered in 75 year-old subjects whose audition is pertaining to age"

Furthermore the loss of hearing of tones in the high frequency range in patients nos. 6 and 7 in group I was more marked than that otherwise seen in patients whose hearing is impaired because of age In four patients (nos. 1 3 and 4 in group I and no 1 in group IV) the loss of hearing applying to the low frequency range was also of a more severe degree than otherwise seen among patients whose hearing is impaired because of age

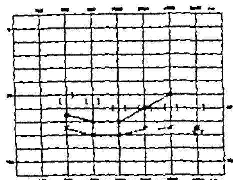


Fig. 9. Hearing curve from the senile patient with Ménière's disease.

throat, but the origin of this complaint could not be defined; an inexplicable paralysis of the right vocal cord was diagnosed.

The patient died at the age of 83 years.

Autopsy inspection of organs disclosed: "Thrombosis a. pulm. sin. et infarctus lobi inf. pulm sin., pneumonia sin. and atrophia fusca et arteriosclerosis organorum m gr.

Microscopy of the right and left temporal bones

The cochleae were sites of bilateral labyrinthine hydrops, most severe on the right side where also the sacculus was involved. The right utriculus was slightly dilated while the semicircular canals appeared to be normal. The tectorial membrane was apparently forced downwards over the organ of Corti. Some areas of Reissner's membrane were of atrophic appearance while proliferation of epithelial cells was in evidence in other areas.

In the right spiral ganglion of the cochlea, the disappearance of cells was of a rather considerable degree at the level of the basal coil, being almost negligible at levels of the middle and apical coils. An even higher degree of disappearance of cells was observed in the left spiral ganglion where it was most pronounced at the level of the basal coil.

In the peripheral part of the right and left acoustic nerves the disappearance of axons was appreciable, being almost of the same order as the disappearance of ganglion cells; remaining axons had degenerated, most markedly on the left side.

The vestibular portions of the labyrinth were of normal appearance on either side which also applied to Scarpa's vestibular ganglion and the vestibular nerve.

Gross inspection of the cerebrum.

(1) A subdural haematoma of long standing was in evidence over the anterior portion of the right cerebral hemisphere.
(2) Diffuse cortical atrophy.
(3) Moderate blurring of the leptomeninges.
(4) Atherosclerotic lesions involving the circle of Willis and extending into the peripheral ramifications.

CHAPTER V

Pathological Processes Involving the Temporal Bone and the Cerebrum in a Senile Patient with Ménière's Disease

The present chapter comprises a review of the past medical history of an 83-year old patient with Ménière's disease together with a summary of the histological findings in the temporal bones and the brain of this patient. The clinical and histological findings are collated with those obtained in similar studies of Ménière's disease as reported in the relevant literature A more detailed account is available in treatise C

The patient was an 83 year-old woman who always had enjoyed a good health, apart from chronic arthritis and moderate dyspeptic complaints

At the age of 50 years, the patient had been hospitalized on account of Ménière's disease manifesting itself as intensifying tinnitus, impaired right-sided hearing capacity and episodes of vertigo She managed to hear speech whispered *ad aurem* and hearing with the left ear remained normal

Episodes of vertigo subsided but her sensations of instability as well as the right sided tinnitus and the ipsilaterally reduced hearing persisted

Ten years later the episodes of vertigo recurred (any detailed data are not available) Hearing with the left ear remained uncharged and satisfactory

At the age of 77 years, i e 27 years after onset of the initial symptoms episodes of vertigo recurred frequently and hospitalization was required. Moreover hearing with her left ear failed and all sounds seemed to be distorted. Audition tests at that time revealed. whispers r/l = aa (ad aurem)/ 0.50 meter speaking voice r/l = aa/3–4 meter

Vestibular irrigation disclosed a severely reduced caloric functioning of both ears Romberg's test was positive when the patient was walking with her eyes closed, she would constantly be deviating to the left. Episodes of vertigo subsided within a couple of weeks A cataleptic attack occurred while she was in hospital.

At the age of 78 years the patient applied for treatment in the State Hearing Centre in Aarhus furthermore, she wanted to have a hearing aid. Audiometry disclosed a severe bilateral deafness of the perception type, cf fig. 9 corresponding to *fig. 1 in treatise C.*

Speech audiometry revealed that the left-sided threshold of intelligibility ranged at 50 db the loss of discrimination ranging at 90 % The patient managed to perceive sounds, but not speech with her right ear She complained of non-gyratory vertigo and besides a high pitched tone persisted in both ears. She was supplied with a hearing aid but she had no benefit from it and returned it

At the age of 79 years the patient consulted an otologist because of a sore

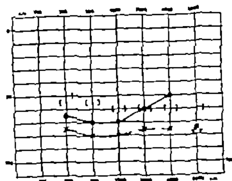


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The patient died at the age of 83 years.

Autopsy inspection of organs disclosed: "Thrombosis a. pulm sin. et infarctus lobi inf. pulm sin. pneumonia sin, and atrophia fusca et arteriosclerosis organorum m gr.

Microscopy of the right and left temporal bones.

The cochleae were sites of bilateral labyrinthine hydrops, most severe on the right side where also the sacculus was involved. The right utriculus was slightly dilated while the semicircular canals appeared to be normal. The tectorial membrane was apparently forced downwards over the organ of Corti. Some areas of Reissner's membrane were of atrophic appearance while proliferation of epithelial cells was in evidence in other areas.

In the right spiral ganglion of the cochlea, the disappearance of cells was of a rather considerable degree at the level of the basal coil, being almost negligible at levels of the middle and apical coils. An even higher degree of disappearance of cells was observed in the left spiral ganglion where it was most pronounced at the level of the basal coil.

In the peripheral part of the right and left acoustic nerves the disappearance of axons was appreciable, being almost of the same order as the disappearance of ganglion cells: remaining axons had degenerated, most markedly on the left side.

The vestibular portions of the labyrinth were of normal appearance on either side which also applied to Scarpa's vestibular ganglion and the vestibular nerve.

Gross inspection of the cerebrum.

(1) A subdural haematoma of long standing was in evidence over the anterior portion of the right cerebral hemisphere.
(2) Diffuse cortical atrophy.
(3) Moderate blurring of the leptomeninges.
(4) Atherosclerotic lesions involving the circle of Willis and extending into the peripheral ramifications.

Microscopy of the central auditory pathways.

Severe degrees of disappearance and degeneration of axons in both acoustic nerves, but most pronounced in the left. The auditory pathways and nuclei were sites of severe outfall and degeneration of ganglion cells and axons Ganglion cells in both auditory centres had also disappeared and degenerated the disappearance and degeneration of myelin sheaths and axis cylinders in the white matter were of a similar severe degree

Microscopy of the central vestibular pathways and centres.

The glial part of the vestibular nerves on both sides had degenerated The course of nerves between the restiform body and the nucleus of the spiral tract of the trigeminal nerve could not be reliably followed The lateral medial and superior vestibular nuclei on either side displayed excessive disappearance and severe degeneration of ganglion cells, the phenomenon being most marked on the left side

Furthermore, severe diffuse degeneration of nuclei and pathways throughout the brain stem was demonstrable in this patient lesions seemed to be most pronounced in the vestibular parts of the nuclei of the cranial nerves

Vessels in the brain stem and the cerebrum displayed signs of capillary fibrosis, arteriolosclerosis, and atherosclerosis.

Thus, in this 83 year-old patient who since the age of 50 years had been suffering from Ménière s disease and in whom an additional loss of hearing of high tones had been ascertained when she was 77 years old findings included

(1) Bilateral labyrinthine hydrops
(2) Degeneration and disappearance of neural elements in the acoustic nerves, parallel to features in the corresponding spiral ganglion of the cochlea and most pronounced on the left side
(3) A normal left Scarpa s ganglion (the one on the right side was not included in the sections) and a rather mild degree of degeneration of axons in the Schwann part of both vestibular nerves
(4) Disappearance and severe degeneration of structures in auditory as well as vestibular central nuclei and pathways

Discussion

The clinical and histopathological findings in this patient shall be briefly discussed and be related to findings obtained in previous works by other investigators

A Lesions involving the epithelial portion of the labyrinth

(1) *Labyrinthine hydrops*

Mygind & Dederding (1938) were the first who recognized that changes in the endolymphatic pressure might be responsible for various degrees of hearing loss applying to the low frequency range when episodes of Ménière s disease occurred

this hypothesis has later been corroborated by experiments on models as well as in animals (*Tonndorf* 1957 *McCabe & Wolsk*, 1961) *Arslan et al.* (1963) arranged sodium chloride crystals on the round window in man, thereby changing the pressure in the labyrinth this procedure would be followed by a development of typical attacks of Ménière s disease in the patient concerned.

On the assumption that the intralabyrinthine hydrops was the exclusive cause of the patient s loss of hearing, audition should be expected to be reduced to a degree paralleling the degree of distension of Reissner s membrane. In the case at issue however audition was best preserved in the right ear in which hydrops was most severe and most widespread. Furthermore hydrops was unilateral and involved the sacculus in one senile patient (no 7 in group I) discussed in chapter IV this patient did not present symptoms of Ménière s disease whereas his loss of perceptive hearing, confined to the high-frequency range, was symmetrical. Also the loss of discrimination was equal on both sides This invalidates the theory that hydrops *per se* was solely responsible for the hearing loss applying to the low-frequency range

Descriptions of labyrinthine hydrops associated with dilatation of the sacculus are on record (*Rollin* 1940· *Kristensen* 1961) In the patient here concerned, dilatation of the sacculus was of an unilateral nature while hydrops in the cochlear coils was bilateral.

(2) *Injury to the organ of Corti*

Pathological lesions of the organ of Corti as well as their importance for audition are not easy to evaluate *Schuknecht* (1953) and *Kristensen* (1961) observed in their patients with severe hydrops that the pathological processes were most pronounced in the apical coil and thus, might account for the hearing loss applying to low tones On the other hand, *Lindsay & Schulthess* (1958) found that the organ of Corti seemed to be fairly normal at the site of the apical coil whereas the loss of ganglion cells in the same area was rather appreciable In patients with Ménière s disease however there will always be some recruitment which serves to confirm that the function of hair cells is reduced (*Dix et al* 1948 *Hood* 1961)

In the present case it could not be reliably ascertained whether the changes in the organ of Corti were more severe than those otherwise seen in cases of presbycusis in patients of equivalent ages (chapter IV) on the contrary sections from all coils gave evidence of a surprisingly well-preserved organ of Corti.

(3) *Changes involving the remaining epithelial structures in the middle scale*

According to available reports, specific changes of supporting cells in the cochlea, the vascular stria, the basilar membrane, and the tectorial membrane, have not been observed in patients with Ménière s disease and were not seen either in the present case

(4) *Changes involving the epithelial portion of the peripheral vestibular organ*

Endolymphatic hydrops in the semicircular canals has never been observed in patients with Ménière s disease and the utriculus is rarely involved (*Hallpike &*

Cairns 1938 *Rollin* 1940 *Lindsay* 1960 *Kristensen* 1961 1962) Electron microscopy revealed lesions involving the superficial layers of the sensorial ephithelium in the ampullae of the semicircular canals (*Pietrantoni & Iurato* 1960 *Litton & Lawrence* 1961) The latter authors held that the pathological changes had been in evidence prior to death and also that the process responsible for the development of Ménière s disease might bring about a cytotoxity that was seen to persist almost until cell death accordingly the peripheral vestibular function would be reduced, it might even be discontinued

It seems rather difficult, however to explain the intensive vestibular symptoms solely as sequelae of the pathological processes in the labyrinth *Busanny-Caspari & Matzker* (1960) did not observe any signs of hydrops in a lateral semicircular canal which was removed at the moment when the patient had a severe attack of Ménière s disease Moreover *Lindsay* (1960) found vestibular reactions to be normal in patients with highly advanced hydrops Even so *Lindsay* postulated that the vestibular reactions to occur during attacks are best explained on the assumption of an existence of a factor of mechanical nature which may upset the ampullary mechanism in one or more ampullae

Apart from the moderate dilatation of the right utriculus, pathological processes in the vestibular portion of the labyrinth were not in evidence in the patient here discussed

B Changes involving the neural elements of the labyrinth

(1) *The auditory portion of the labyrinth (1st neurone of the auditory pathways)*

Several authors have observed in patients with Ménière s disease that the pathological processes in ganglion cells in the apical cochlear coil paralleled the loss of hearing of tones in the low frequency range (*Rollin* 1940 *Lindsay & Schulthess* 1958 *Lindsay* 1960 *Kristensen* 1961) Such hearing loss has been produced in cats via lesions induced to the apical cochlear coil (*Schuknecht & Neff* 1952)

In the patient at issue ganglion cells in all cochlear coils were found to be damaged mainly those in coils of the left cochlea the latter is commensurate with the fact that her hearing on the left ear was most severely impaired In contrast, in the senile patients discussed in chapter IV (groups I II and III) the hearing impairment as well as the pathological processes were symmetrical

Disappearance and degeneration of neural elements were also found to be most intense in the peripheral part of the left cochlear nerve where it paralleled the degree of disappearance of ganglion cells in the spiral ganglion of the cochlea.

Dandy (1937) observed usually a large arterial branch in touch with the cochlear nerve in patients with Ménière s disease This phenomenon was not observed in our patient

(2) *The vestibular portion of the labyrinth (1st neurone of the vestibular pathways)*

The incongruity between the, often severely reduced caloric vestibular reaction and the histological findings in the vestibular portion of normal labyrinths represents

an outstanding phenomenon which has been observed previously by other investigators (e g. *Kristensen* 1961) as well as by the present author

C Changes involving the cerebral cochlear and vestibular neurones

(1) *The auditory pathways and centres*

A review of the relevant literature as well as the clinical data obtained (chapter IV) suggest that a loss of hearing of tones in the low frequency range may represent the sequelae of lesions involving sites centrally to the cochlea, either in the auditory nerve or in the brain stem. *Lundborg* (1955) *Gravendeel* (1958), *Gravendeel & Plomp* (1960), and *Parker et al* (1962) have advanced the same hypothesis.

In the patient here discussed, changes of the ganglion cells in the 1st neurone were not sufficiently marked to represent the factor exclusively responsible for the loss of hearing, whether of tones in the low- or high-frequency range accordingly such hearing loss must be attributable to factors localized to central sites considering the histological findings in the central auditory pathways, the latter seems most probable

(2) *The vestibular pathways and centres*

Reports concerning histological studies of the cerebral vestibular neurones in patients with Ménière s disease are not available. Electronystagmographic curves obtained in cases of this disease have revealed, however some features suggestive of cerebral lesions (*Aschan & Stahle* 1957 *Montandon* 1959 *Maspétiol et al.* 1961) This finding has been corroborated by *Rossberg* (1960) and *Maspétiol et al.* (1962) who for instance, on the basis of clinical deliberations suggested that the vegetative and nystagmogenic centres in diencephalon might be affected in patients with Ménière s disease Stimulation of the hypothalamus in cats has been found to change the rate of velocity of blood perfusion in the cochlea (*Morizono* 1966). Thus inspired, it might be worthwhile to consider whether irritative disorders in the central nervous system might exert an influence on the pressure in the internal ear

In the patient here concerned, the extremely severe lesions involving the central estibular nuclei and pathways were by far more intense than those in the other structures of the brain stem the latter is in contrast to the fact that the peripheral neurones remained well-preserved.

(3) *Additional cerebral lesions*

Several authors have observed neurological symptoms other than those pertaining to Ménière s disease, indicating a presence of cerebral lesions. According to *Crowe* (1937) the patients might become unconscious, diplopia of transient nature might occur and occasionally the corneal sensitivity on the same side as the audio-vestibular symptoms might be reduced. *Podvinec et al.* (1961) observed paralysis of the trigeminal nerve associated with endolymphatic hydrops, in 9 out of 18 patients In one patient, Bell's paresis was seen to develop coincidentally

with the primary episode of Ménière s disease *Greiner et al* (1954) saw one patient in whom the lesion developed along with syringomyelia

The patient here concerned had cataleptic attacks, unilateral paresis of the vocal cord, positive Romberg s symptom, and besides, she would constantly be deviating to the left if she were walking with her eyes closed symptoms which all may be attributable to diffuse cerebral lesions

Furthermore some authors have suggested that the aetiology of Ménière s disease might include cerebral vascular lesions and accordingly that "vascular crises" might be responsible for the sporadically occurring symptoms For instance, symptoms of Ménière s disease have repeatedly been observed in patients whose complaints might be ascribable to vascular diseases such as Quincke s oedema (*Dederding* 1929) glaucoma (*Godtfredsen* 1949 *Hilger* 1950) migraine (*Sørensen* 1959) lesions of the conjunctival vessels (*Naito* 1962) and extensive vascular disorders exciting symptoms of transient nature in the trigeminal nerve and the facial nerve" (*Podvinec et al* 1961)

In the present case, the vascular changes were never seen to be of a degree more severe than that otherwise seen in senile patients like the ones discussed in chapter IV especially not the lesions at the site of the circle of Willis.

It emerged from the review of the literature that opinions of and views on the localization or localizations, of the pathological processes responsible for a development of Ménière s disease were highly conflicting

On the basis of the histological findings in the patient here concerned it may be presumed that her symptoms were due to lesions at peripheral as well as central sites, mainly to those at central sites Whether the patient s loss of hearing of high tones is to be taken as a symptom of Ménière s disease or it was due rather to her age and the severe arteriosclerosis, remains to be decided, but the pathological findings suggest that her hearing loss applying to the high-frequency range originated in lesions at peripheral and especially at central sites

PART 2

Studies of Vessels in Temporal Bones after Injection of Contrast Medium

The subject matter of Part 2 is the results obtained by injection of contrast medium into vessels of human temporal bones. The primary object was to investigate whether vessels in the membraneous labyrinth have to pass a capillary system before they come into communication with vessels in the surrounding osseous structures. Another object was to describe the anatomy of the vascular pattern in the cochlea and the acoustic nerve in subjects at various ages, in an attempt to defining the aetiology of the lesions discussed in Part 1

Chapters VI VII VIII and IX are abstracts of the previously published treatises D E, F and G chapter X contains a summary of all findings obtained and discussed in parts 1 and 2 and the ensuing conclusions

CHAPTER VI

Material and Methods

The material comprises 43 temporal bones from a total of 33 individuals at ages ranging between five days and 94 years.

Any selection of specimens has not been possible the material comprises 11 temporal bones from 11 "unclaimed bodies" autopsied in the Los Angeles County Hospital, together with 32 temporal bones from 23 patients who died in Odense Amts og Bys Sygehus (the University Hospital in Odense)

The group termed unclaimed bodies" comprises the bodies of patients who died in the Los Angeles County Hospital or had been brought into the hospital with a view to post-mortem examination and subsequent embalming. The clinical findings were not specified. According to a rough estimate based on data provided by the pathologist, ages of these subjects ranged above 50 years the sex of patients is not on record The author removed the first specimens, but received later temporal bones that had been removed by members of the staff trained for this purpose.

After moving to Odense, the author removed specimens from patients there. Temporal bones were obtained from 7 women and 15 men. The ages of patients were as follows One 5-day-old boy (premature by two months) the age group 20–29 years included one man the age group 40–49 years included two women and one man the age group 50–59 years two women and three men, the age group 60–69 years one man the age group 70–79 years, two women and four men the age group 80–89 years one woman and two men, finally two men were 92 and 94 years old, respectively Audiological and otological examinations had been performed in three of these cases reduced hearing of the presbycousis type was diagnosed in all three

The patients died of diseases which had not affected the temporal bones *except* in cases where the pathological changes were sequelae of generalized arteriosclerosis

As egards patients who died in the Odense hospital, the bodies were transferred to the morgue about 6 hours after death and kept there at about −5 C. The patients who died in Los Angeles were also kept in the morgue, but intervals between death and transfer to the morgue might be of varying lengths.

The temporal bones were removed as soon as possible after death in the case of bones obtained from patients in Los Angeles, they were removed about 24–48 hours after death, but prior to embalming. Temporal bones from patients who died in the Odense Hospital were removed at intervals after death ranging between 7

The temporal bones were removed and prepared in accordance with the follow ing method elaborated by the author (cf. treatise D)

1 The cerebral hemispheres were tilted backwards The tentorium cerebelli was cut as close as possible to the superior petrosal sinus The cranical nerves I–VI and the internal carotid arteries were bisected, upon which the cerebral hemispheres could be everted further backwards
2. Prior to further dissection the anatomy of vessels and nerves in the cerebello-pontine region was studied As to the series originating in Odense a substance with a particle size of 0 1 micron in 1 % aqueous solution (Lichtblau 2 R 'Bayer") was injected in order to facilitate identification of vessels and, if possible, to make photographic studies The results obtained in these experiments (unpublished data) were submitted in a lecture read to the "Inter national Course in Transtemporal Microsurgery of the Internal Auditory Canal" Zürich, March 1970
3 The glial part of nerves VII and VIII was cut at the site of their entrance into the brain stem Furthermore, about 3–4 cm from the medial orifice of the internal auditory canal and the subarcuate fossa, the vascular system which enters into the temporal bone from the posterior surface of the petrosal part was cut off In order to have a sufficiently large vascular section available for the later injections part of the cerebellum was usually included. The mass of tissue thus produced was cautiously covered by gauze which served as protection during removal of the temporal bones
4 Care was taken to spare the temporal bone squama while the petrosal part, portions of the mastoid process the middle ear and the medial portion of the external auditory canal were removed The damage thus inflicted to the base of the skull was trifling and both temporal bones could be excised
5 The specimens were immersed in physiological saline and taken to the laboratory where they either immediately or after storage in the refrigerator at about —4 C for some days were kept in a specific holder designed by the author and built by Jack Urban, Urban Engineering Co Burbank, California. It is an advantage of this holder that it permits dissection from all angles (cf fig 2, treatise D) moreover fitting of a small platform makes it possible to keep the aforementioned mass of vessels and nerves level with the medial orifice of the internal auditory canal. Fitting of another specially designed equipment for vascular injections permitted delicate manipulation and sufficient stability
6 A surgical microscope was used while a syringe was inserted into the vessel or vessels into which injections were applied. All other vessels were com pressed by micro-bulldog clamps Subsequently the injections could be applied without wasting much of the contrast medium

According to the experience gained by the author the time interval between death and removal of temporal bones as well as the interval between removal of bones and injection of contrast medium, were of no significance for the results to be obtained

Vessels were traced in accordance with the following techniques.

a. Injection of "Microphil" (Canton-Bio-Medical Products, Canton, Mass.)
b. Injection of suspensions of various porcelain dyes, namely sulphides containing circular grains of sizes ranging between 0.5 and 1 micron in 10 % gelatine. The suspensions were prepared by the author.
c. Histochemical demonstration of the alkaline phosphatases of vascular walls, thereby reproducing the vessels in a distinct, reddish-violet contrasting colour. Initially the enzyme in the vascular walls had been fixed by injection throughout 30 minutes into the specimen, using buffered (pH about 7) formalin calcium (1 % $CaCl_2$ in 4 % formaldehyde) at room temperature, immediately followed by continued injection throughout 30 minutes of about 10 ml of Burstone's azo-solution for the staining of alkaline phosphatases.

The solution was prepared as follows:

(a) Naphthol As-Bi phosphoric acid (Sigma Chemical Company) 4–5 mg dissolved in 0.25 ml of N N-dimethyl formamide
(b) addition of 5 ml of distilled water
(c) addition of 5 ml of 0.2 mol Tris buffer (pH 8.3–9.0)
(d) addition of 30 mg of Red Violet LB in the form of diazonium salt followed by vigorous shaking of the mixture
(e) the incubation medium was filtered and immediately injected into the specimen

The result appeared in the form of a reaction product of a reddish-violet colour.

Since the reddish-violet colour might be rather close to the bluish violet colour which at the subsequent microscopy of the specimens was seen to develop as an optic error, a solution comprising exclusively formol calcium, but no subsequent injection of azo-dye, was injected into one control specimen (not included among the above mentioned 43 specimens).

All of these solutions (a, b, and c) were preferably injected under physiological pressure, oscillating between systolic and diastolic rates of pressure. Injections into temporal bones from unclaimed bodies were applied at pressures ranging around 150 mm mercury, owing to the lack of data concerning these patients.

In the case of solutions of type "a", processes of injection covered 15 minutes, covering 30 minutes in the cases of types "b" and "c".

In some temporal bones differently coloured contrast media were injected into various vessels in order to demonstrate vascular anastomoses, if any, between the individual vascular systems into which injections had been applied. In order to demonstrate whether anastomoses between the basilar artery and branches of the carotid artery were in evidence, a dye material was injected into seven temporal bones via branches of each of the two arterial systems. Injection into branches of the carotid system was performed in the autopsy room after the common carotid artery had been clamped at the site inferior to the site of injection, the internal carotid artery was clamped at an intracranial site close to the cavernous

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6 A surgical microscope was used while a syringe was inserted into the vessel or vessels into which injections were applied All other vessels were com pressed by "micro-bulldog clamps Subsequently the injections could be applied without wasting much of the contrast medium

According to the experience gained by the author the time interval between death and removal of temporal bones as well as the interval between removal of bones and injection of contrast medium, were of no significance for the results to be obtained

8 Decalcification by an 0 7 M solution of the tetrasodium salt of EDTA, pH 7 4 at 37 Decalcification was discontinued as soon as X-ray control had showed that all calcium was eliminated, usually after decalcification for 2 or 3 months.

9 Dehydration in rising concentrations of ethyl alcohol (25 %–50 %–70 %–96 / absolute alcohol) over a period of one week.

10 Embedding in celloidine at room temperature (2 /–6 /–12 /) usually throughout 2 or 3 months, followed by hardening in 70 / ethyl alcohol for one week.

11 Mounting of specimens onto cutting blocks by means of 10 % celloidine followed by hardening in 70 / ethyl alcohol, lasted for about 1 week subsequently the blocks were cut into sections of a thickness ranging from 500 up to 800 micron. The sections tolerated storage for an unlimited time until the further processes were to be performed

12 The celloidine was removed by equal portions of ether and absolute alcohol two treatments in this fluid were generally used, each covering 2 or 3 hours

13 Clearance of sections in methyl salicylate

14 With a view to a further cutting of these thick sections into thinner ones (cf procedure described in treatise G), the aforementioned embedding in celloidine was repeated and the blocks were cut into sections measuring 7 micron

15 Additional staining by routine histochemical methods such as haematoxylin combined with periodic-acid-Schiff (PAS) or toluidine blue.

Specimens in which essels had been reproduced by staining of the vascular walls *per se* using alkaline phosphatase reagents, were further dissected as follows:

a The bone was removed by a diamond drill until nothing but a shell of bone measuring a few millimeters across surrounded the membraneous labyrinth.

b Subsequent decalcification with R.D O (Trade Mark Bethlehem Steel Corp) for 10 hours at room temperature

c Cutting on the freeze-microtome into sections measuring 25–30 micron.

d Embedding in gelatine jelly

As regards the preparation of the thick, cleared sections, the above technique has been used previously by other investigators, for instance, *Eichler (1910)* *Levin A A* (1964) and *Levin V N* (1969)

Note Application of this technique was suggested to the author by Dr William House M D Los Angeles, who also supported the decalcification project by means of a grant placed at disposal at the meeting of the Otological Medical Foundation in July 1967 Specimens were forwarded to the University Clinic in Odense where the author supplemented the series with specimens into which more than one dye material had been injected.

N te The vascular nomenclature used in the ensuing chapters is the one introduced by *Axelsson* (1968)

sinus In addition the superior thyroid artery the lingual artery and the external maxillary artery were compressed. Great quantities of the contrast medium were wasted during this process and the pressure could be maintained only at a level which on an estimate ranged below 100 mm/mercury injections were applied over time intervals covering about 2 minutes During injection, the anterior and the posterior surfaces of the petrosal part of the temporal bones were observed When injections had been in progress for a few seconds the contrast medium would appear below the dura mater in the area surrounding the geniculate ganglion Injections were not discontinued until dural vessels in the posterior surfaces probably also the subarcuate artery had been filled via structures in the temporal bone Two of the temporal bones were left without a second injection via branches of the basilar artery they were to serve as controls

The entire material has been classified according to the vessel or vessels into which injections were applied as well as according to type of medium used for the injections

		Nos. of specimens
I	Injection via a.i c.a (anterior inferior cerebellar artery) Microphil	28
II.	Injection via a i.c.a 10% gelatine suspension	2
III	Injection via a i c.a alkaline phosphatase reagent	1
IV	Injection via the common carotid artery exclusively Microphil	1
V	Same as item IV except that a 10% gelatine suspension was used	1
VI	2 injections (1) 10% gelatine suspension into the common carotid artery (2) Microphil via a.i.c.a.	1
VII	2 injections (1) Microphil via the common carotid artery (2) Microphil via a.i c.a.	3
VIII	2 injections (1) Microphil via the carotid artery (2) alkaline phosphatase reagent via a.i c.a.	3
IX.	2 injections of Microphil (1) via the subarcuate artery (2) via the the internal auditory artery	2
X	2 injections (1) Microphil via a.i.c a (2) Microphil via the inferior petrosal sinus	1
	In total	43

7 After injection of contrast medium the specimen concerned was immersed into a 3 7 % solution of formaldehyde buffered with marble All specimens except those to which alkaline phosphatase reagent had been applied were thoroughly perfused throughout 30 minutes with an 0.5 % solution of osmic acid applied via an orifice in the superior semicircular canal and the round window As a result of this process the epithelial structures of the labyrinth and the mucous membrane of the middle ear would be stained a brownish black colour that contrasted the injected dye materials

Specimens into which Microphil and/or 10 % gelatine suspensions had been injected were prepared as follows

8. Decalcification by an 0 7 M solution of the tetrasodium salt of EDTA pH 7 4 at 37 Decalcification was discontinued as soon as X ray control had showed that all calcium was eliminated, usually after decalcification for 2 or 3 months.
9. Dehydration in rising concentrations of ethyl alcohol (25 %–50 %– 70 %– 96 % absolute alcohol) over a period of one week.
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11. Mounting of specimens onto cutting blocks by means of 10 % celloidine, followed by hardening in 70 % ethyl alcohol, lasted for about 1 week subsequently the blocks were cut into sections of a thickness ranging from 500 up to 800 micron. The sections tolerated storage for an unlimited time until the further processes were to be performed.
12. The celloidine was removed by equal portions of ether and absolute alcohol two treatments in this fluid were generally used, each covering 2 or 3 hours
13. Clearance of sections in methyl salicylate.
14. With a view to a further cutting of these thick sections into thinner ones (cf procedure described in treatise G) the aforementioned embedding in celloidine was repeated and the blocks were cut into sections measuring 7 micron
15. Additional staining by routine histochemical methods such as haematoxylin combined with periodic acid Schiff (PAS) or toluidine blue

Specimens in which vessels had been reproduced by staining of the vascular walls *per se* using alkaline phosphatase reagents, were further dissected as follows

a. The bone was removed by a diamond drill until nothing but a shell of bone measuring a few millimeters across, surrounded the membraneous labyrinth.
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X	2 injections. (1) Microphil via a i c.a. (2) Microphil via the inferior petrosal sinus	1
	In total	43

7 After injection of contrast medium the specimen concerned was immersed into a 3 7 % solution of formaldehyde buffered with marble All specimens except those to which alkaline phosphatase reagent had been applied were thoroughly perfused throughout 30 minutes with an 0.5 % solution of osmic acid applied via an orifice in the superior semicircular canal and the round window As a result of this process, the epithelial structures of the labyrinth and the mucous membrane of the middle ear would be stained a brownish black colour that contrasted the injected dye materials.

Specimens into which Microphil and/or 10 % gelatine suspensions had been injected were prepared as follows

ally separates the inferior portion of the fundus in the internal auditory canal from the middle ear

Some authors have demonstrated the presence of vascular anastomoses between intra- and extra-labyrinthine structures. For instance, anastomoses between the promontorium and the internal ear could be followed in specimens stained with osmic acid (*Politzer* 1876) and also by a study of serial histological sections (*Siebenmann, 1894*) *Zange* (1919) and *Hansen* (1967) managed to trace a few vessels which via the bone separating the basal and middle cochlear coils connected the promontorium of the middle ear with the modiolus of the inner ear. Finally *Börner and Pivotti* (1954) and *Morujo* (1967) described anastomoses to the otic capsule via branches of the internal auditory artery localizations of such anastomoses were not further specified.

In patients with otosclerotic foci involving the endosteal layer of the cochlear capsule, for instance *Altmann* (1962) observed that such foci might invade the septa which separate the cochlear coils. It was emphasized in particular that the blood supply to the cochlea might be compromised if these foci penetrated into the bones separating the basal and the middle coils. *Ruedi* (1968) demonstrated the presence of venous anastomoses between otosclerotic foci and the membraneous labyrinth, in particular at the site of the basal coil. *Kelemen and Linthicum Jr* (1969) declared that hearing loss of the perception type would occur in patients in whom the basal cochlear coil, maybe also several other coils, were infiltrated by otosclerotic foci

According to reports available in the literature, it seems as if infiltration by otosclerotic foci via the otic capsule or via the bony shelf separating the basal and middle coils, might be responsible for a reduced cochlear function. It is also apparent from the cited literature that the bone structure of the basal coil, particularly the structure separating the basal and middle coils, occupies an exceptional position, whether considered from embryological, bone-morphological, vascular-morphological, histopathological or functional points of view

Within the cochlear modiolus, the basal portion, i.e. the *portion facing* the osseous shelf by which the basal and the middle coils are separated, seems to be vascularized to a higher degree than those at more apical sites. *At the former site*, the cochlea is supplied mainly by the spiral modiolar artery as well as by the cochlear branch of the vestibulo-cochlear *artery* whereas vascularization at apical sites, via the spiral modiolar artery is less abundant (*Axelsson* 1968). This anatomical feature intensifies further the impression *that* the cochlear function seems to be mainly dependent on the vascular supply to the *basal coil*.

Some reports have been concerned with a description of areas in the vestibular part of the labyrinth where the endosteal *layer either* may be absent or be very thin, thereby opening up possibilities of an anastomosing between the membraneous labyrinth and the enchondral layer *of the labyrinthine* capsule. *Siebenmann* (1894) observed areas of this type at the non-ampullary end of the three semicircular canals According *to Werner (1931)*, such defective areas might develop during foetal life as a result of resorption and destruction of the convex portion of the semicircular canals during growth of the latter In agreement with this, *Bast*

CHAPTER VII

Vascular Anastomoses Between the Membraneous Labyrinth and the Surrounding Structures

Vessels in the membraneous labyrinth of the temporal bone have hitherto been considered end-arteries which, by an endosteal capsule seem to be cut off from vessels in the surrounding bone (*Seymour* 1954 *Arslan* 1963 *Anson et al* 1966) By now however it is generally agreed that numerous vessels communicate with the surrounding tissues during foetal life and throughout the first two or three years of life namely before the endosteal layer has fully developed (*Zange* 1919 *Bast* 1942 *Levin* 1964 and *Anson et al* 1966)

As to the viability and thus the vascularization, of the endosteal layer *per se* some doubt is still prevailing. For instance, *Rius and Mendoza* (1961) and *Sërcer and Krmpotić* (1966) declared that this layer was non viable while *Rüedi* (1963) held that the endosteal layer was supplied from a branch of the auditory artery *Zechner and Altmann* (1969) agreed with the latter in that the said layer was vascularized although poorly *Gussen* (1968) found that it might be an expression of a certain viability that the tissue lining the endosteal layer facing the membraneous labyrinth contained mesenchymal cells, including osteogenic as well as chondrogenic properties which feature might be encountered even in aged individuals

Several authors have discussed the defects which throughout life may involve certain areas of the endosteal layer Such defects might provide a possible inter communication between the membraneous labyrinth and the intermediate, more richly vascularized enchondral layer of the otic capsule These authors attached special interest to the latter sites because they might allow invasion of inflammatory processes into the membraneous labyrinth (*Politzer* 1876 *Siebenmann* 1894 *Eichler* 1910 *Zange* 1919 *Eckert Möbius* 1926 *Meyer* 1933)

In the cochlear portion of the labyrinth it is mainly a matter of bone structures which throughout the length of one coil, seem to be inserted like a coarse meshed osseous shelf between the basal and the middle coils thereby connecting modiolus with the enchondral layer of the otic capsule One of the first processes of ossifica tion to develop during foetal life originate from areas at the site of the basal portion of this bone-shelf (*Bast and Anson* 1949) The separation between the tympanic scale and the vestibular scale is initiated at this site of ossification As previously mentioned the bone structure in the basal coil of this osseous separa tion is rather loose in contrast to that at more apical sites, the structure of which is dense Basally the shelf is seen to widen until it joins with the bone area which antero-posteriorly separates the cochlea and the vestibulum while it medio-later

artery the direct extensions of the intraneural vessels of the cochlear nerve as well as via the osseous branches through which the osseous bridge between the basal and middle coils communicated with vessels in the enchondral layer of the otic capsule Thus arterial connection with at least four different vascular areas was demonstrable, whereas the capillary system pertaining to the neural elements of the middle and apical coils presented only two affluxes and effluxes in the capillary system facing the neural elements of the middle and apical coils, namely via the spiral modiolar artery and the intraneural vessels in the acoustic nerve

Vessels in the basilar membrane were also found to be well-filled, especially within the basal coil. It was rather remarkable that vessels in the basilar membrane were filled even in areas where disappearance and degeneration of internal and external hair cells in the organ of Corti, reproduced by means of osmic acid, were of severe degree The feature was in evidence for instance in the temporal bones from old patients with presbycousis.

Owing to the fact that degrees of filling differed greatly from specimen to specimen and that the relative filling might differ in medial cochlear structures (modiolus and basilar membrane) and lateral cochlear structures (vascular stria) it proved impossible to draw any conclusions concerning the distribution of passable vessels in structures of the middle scale in patients of different ages On the other hand, numerous parallel capillary anastomoses between the vascular stria and the basilar membrane, by way of Reissner's membrane, were in evidence in a temporal bone from an about 90-year-old patient; a yellow dye material, grain size about 0 5 micron, suspended in gelatine solution had been injected into the bone via the common carotid artery (cf. fig. 6 in treatise B.)

B Anastomosis via the endosteal layer between the membraneous cochlea and the otic capsule

The vascular anastomoses were found to be of two types (and two calibres), one in the form of osseous branches of calibres approximating those of arterioles and originating either from radiating arterioles of the vestibular scale or communicating with the collecting venules of the tympanic scale, the other in the form of nutritional canals or capillaries of especially small calibres, interspersed in the dense network of osseous lamellae in the endosteal layer

These rami ossiculorum arteriolae rectae were demonstrable in 15 specimens Each specimen contained only few (1–3) which all were of the same calibre as the radiating arterioles from which they emerged. They might emerge from any site throughout the course of the latter even from sites at which they joined with the capillary system of the vascular stria. The anastomoses were evenly distributed over the cochlear coils.

In 14 bones, the injected medium had penetrated into spaces (calibres less than 1 micron) between the web-like system of osseous lamellae in the endosteal layer Mostly it was seen at the level of the apical and the middle coils. In some specimens, the dye material had penetrated via the long and tortuous pathway

(1942) observed the occurrence of such resorption peripherally in the semicircular canals

Several authors, for instance *Manasse* (1905) and *Zange* (1919) observed a strand of connective tissue between the ampullae of the posterior semicircular canal and the tympanic recess close to the round window Indeed, this might be another site through which inflammatory processes might have access and where vascular anastomoses between the membraneous labyrinth and its surroundings could be found.

Author's experiments and results

The results obtained have been described and discussed as follows in treatise E.

A Anastomosis directly uniting the membraneous cochlea and the enchondral layer

Among the 40 bones which were cut into sections of a thickness ranging between 500 and 800 micron, 31 presented anastomoses of arteriolar calibre via the osseous shelf by which the basal cochlear coil is separated from the middle coil, namely anastomoses between modiolus and the enchondral layer of the otic capsule

In all 31 cases, the injected medium was seen to penetrate to this level, or further apically in the cochlea In the remaining nine specimens, injection was very sparse and the injected dye material failed to reach into the said area of the cochlear capsule

The above mentioned anastomosing vessels into which injections were applied were arteries as well as veins which individually intercommunicated with the capillary plexus surrounding the cochlear spiral ganglion The anastomoses emerged either directly from the spiral modiolar artery or they communicated directly with the two large spiral veins at other sites, however a middle piece might be inserted Such a middle piece could be seen to unite with arterioles to the basilar membrane structures radiating arterioles to the vascular stria, and furthermore anastomosing vessels of arteriolar calibre which emerged directly into the enchondral layer of the osseous capsule Arterio-venous intercommunications were also demonstrable in the modiolus at the base of the aforementioned anastomoses between modiolus and the otic capsule Thus, the pattern by which the vascular system united the modiolus with the enchondral layer appeared to be highly polymorphous In each specimen, the number of vascular anastomoses of arteriolar calibre ranged, roughly between five and ten the number of vessels into which contrast medium was injected and that of identifiable vessels stained by osmic acid have been added

The following features emerged from a more detailed analysis of the modiolar vascular system axially to the ingress or egress of the osseous anastomoses, including the capillary plexus surrounding the cochlear spiral ganglion At basal sites of the modiolus, afflux and efflux progressed via the following groups of vessels, the spiral modiolar artery the cochlear branch of the vestibulo-cochlear

artery the direct extensions of the intraneural vessels of the cochlear nerve as well as via the osseous branches through which the osseous bridge between the basal and middle coils communicated with vessels in the enchondral layer of the otic capsule. Thus arterial connection with at least four different vascular areas was demonstrable, whereas the capillary system pertaining to the neural elements of the middle and apical coils presented only two affluxes and effluxes in the capillary system facing the neural elements of the middle and apical coils, namely via the spiral modiolar artery and the intraneural vessels in the acoustic nerve.

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While supplies of blood are most abundant and rates of metabolism highest in the basal cochlear coil, the structures at this site apparently are the ones most sensitive to circulatory disturbances as compared with structures of the more apical coils. This feature has been observed in experiments on guinea pigs exposed to venous obstruction (*Kimura and Perlman* 1956) coagulation of the anterior inferior cerebellar artery (*Kimura and Perlman,* 1958), and obstruction for 30 minutes of the above mentioned arteries and subsequent re-establishment of the circulation (*Perlman Kimura and Fernandez,* 1959).

Whether the observed vascular anastomoses between structures of the membraneous labyrinth and the otic capsule may be of value for the preservation of the integrity of the membraneous structures cannot be judged until it has been defined in greater detail how these anastomoses come into communication with vessels outside the otic capsule for instance, vessels originating from the carotid arteries. The results obtained in studies of these vascular communications are submitted and discussed in chapter VIII

traversing the endosteal layer finally combining with the vascular system of the enchondral layer

In bones in which the medium had been injected via carotid arteries, it could be traced to the endosteal layer which was entered from external aspects thence it would progress further into structures of the membraneous labyrinth, a feature to be discussed in greater detail in the following chapter

C Anastomosis between the membraneous labyrinth and the osseous capsule in the vestibular portion of the labyrinth

In 16 of the temporal bones into which medium had been injected, such direct vascular intercommunication was demonstrable in the non-ampullary part of the superior semicircular canal where the endosteal layer either was very thin or non-existent. In the lateral semicircular canal, however this type of anastomosis was observed only in one specimen

In five specimens, the dye material had penetrated into the fibrous strands by which the ampullae of the posterior semicircular canal communicate with the tympanic cavity

As mentioned in chapter VI injections of grained dye materials were in all cases followed by perfusion of the labyrinth via an orifice in the superior semicircular canal or via the round window (perfusion with 0.5 % osmic acid for 30 minutes) The osmic acid had reproduced the said anastomoses to an extent by far greater than that otherwise obtainable by injection of grained dye material

It should be stressed that the degree of filling to be obtained in these vascular areas was independent of the age of the individuals from whom the specimens were obtained.

Discussion and conclusion

In specimens where the contrast medium had penetrated to the loosely built bridge separating the basal and the middle cochlear coils anastomoses of arteriolar calibres were in all cases found to communicate directly with the enchondral layer of the otic capsule Moreover throughout the cochlear coils, vessels of arteriolar calibre emerged from the radiating arterioles of the vestibular scale or they anastomosed with the collecting venule of the tympanic scale hence the vascular system in the cochlea cannot be considered composed of end-arteries.

The fact that the basal cochlear coil is the site at which anastomosing is most readily established is in further support of the findings by *Axelsson* (1968) who observed that the vascular supply to the modiolus is more abundant in the basal than in the more apical coils.

These anatomical features can be related to those encountered in experiments on guinea pigs in which the consumption of energy in the individual cochlear coils was estimated In experiments of this type *Meyer zum Gottesberge and collaborators* (1965) and *Rauch* (1967) found the rate of metabolism to be highest in the basal coil gradually decreasing towards the apical coil.

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Re Item B

Nager (1954) described the vascular communication between the subarcuate artery and the vascular system of the middle ear the latter system is considered to belong to the carotid system.

Using arteriographic techniques *Djupesland* (1970) managed, in one patient, to trace vessels from the basilar arterial system, via the osseous substance of the temporal bone, to the vascular system in the neck.

Re Item C

According to some authors, the course of vessels could be traced from the membraneous cochlea to the middle ear promontorium (*Politzer* 1876 *Siebenmann*, 1894 and *Zange* 1919) Such anastomoses, however are apparently rare

In a preliminary report on the results obtained by micro-injections into the vascular structures of the temporal bone, *Hansen* (1967) described a technique to be used for dissection the technique included the drilling away of osseous structures immersed into 70 / ethyl alcohol, using a stand which produced a certain transillumination of the specimen, thus, vessels into which injections had been applied could be seen to extend from the promontorium directly to structures of the basal cochlear coil. The author did not find the technique sufficient to be used for a systematic analysis of the vascular pattern in larger numbers of temporal bones and therefore preferred the conventional histological method, as mentioned in chapter VI (Material and Methods)

The results obtained have been discussed in greater detail in treatise F

Author's studies and results

The series of 43 temporal bones is identical with the series discussed in chapter *VII* (Vascular anastomoses between the membraneous labyrinth and surrounding structures) As previously mentioned, all bones were studied consecutively irrespective of degrees of vascular filling. In addition to the morphological data thus obtained concerning the pattern of injections into vessels, it was possible also to decide whether contrast medium penetrated into some areas of bone more readily than into others

In an attempt to demonstrate vascular intercommunication between extra and intra-cranial vessels, between various branches from large vessels known to supply the temporal bone, and between arteries and veins, differently coloured contrast media were injected into one and the same bone *via different* vessels. At the same time it was possible to determine whether cochlea is supplied via extra-cranial vessels as well as via intra-cranial vessels.

Re Item A

In table 3 a parallel is drawn between the degree of filling in one of the areas which according to *Eckert Möbius* (1926) is particularly rich in vessels, namely

CHAPTER VIII

Vascular Anastomoses Within Osseous Structures of the Temporal Bone

In this chapter it is attempted to illustrate the various problems involved in the *anatomy normal as well as pathological of the otic capsule with special regard* to the further course through the latter of the established vascular anastomoses to the membraneous labyrinth (cf chapter VII)

The following topics shall be discussed

A Is *vascularization particularly rich in some areas of the otic capsule?*
B Is it possible to demonstrate anastomoses between the extra and intra-cranial vessels which supply the otic capsule? *Between individual branches emerging* from larger vessels from which branches extend to the temporal bone? Between arteries in the bone substance and the venous sinuses?
C *Are the membraneous labyrinth, the more remotely situated structures of the* temporal bone, and the extra-cranial vessels in vascular communication via the vascular system in the otic capsule?

These topics have according to the available literature been discussed on few occasions only and discussions have mainly been concerned with the pathways which inflammatory processes might follow in their course through the otic capsule (*Politzer* 1876 *Siebenmann* 1894 *Zange* 1919 *Eckert Möbius* 1926 *Meyer* 1933 *Wullstein* 1948 and *Bast and Anson* 1949)

Re Item A

On the basis of a compendium including a review of previously published studies as well as on the basis of personal studies *Eckert Mobius (1926) and later also Bast and Anson* (1949) demonstrated how a richly vascularized connective tissue invades the primitive cartilage of the temporal bone during foetal life *Eckert Möbius* paid particular attention to two areas namely one surrounding the semi circular canals (supplied by branches from the subarcuate artery) the other comprising vessels the course of which extended from *the complex of the internal* auditory artery to the osseous zone separating the cochlea from the vestibulum in the antero-posterial direction and the internal auditory canal from the promontorium of the middle ear in the medio-lateral direction *In the early literature* this zone was termed 'Cozzolino s zone according to *Eckert-Mobius* it is particularly rich in vessels and connective tissue even at late stages during life

it was possible also to follow via the bone substance, the course of vessels from the subarcuate artery and from branches of the internal auditory artery right to the carotid canal. Calibres of these vascular anastomoses were similar to those of arterioles. Furthermore, injections directly into carotid branches made it possible to trace vessels, the courses and calibres of which parallel the former although injections had been applied via the opposite end.

Two dye materials were injected into each of seven specimens, the first being injected via carotid branches, the other via branches of the anterior inferior cerebellar artery (Groups VI, VII, and VIII in chapter VI); the differently coloured media in all cases were found to coincide in vascular lumina the calibres of which were estimated to parallel those of arterioles. This phenomenon is most frequently encountered in the enchondral layer of the otic capsule, but indeed, contrast media appeared also in vessels of the endosteal layer as well as in those in the periosteal layer. The dye materials are traceable from one vascular area to another, even though passage through the capillary system is escaped.

Vascular anastomoses of this type were demonstrable in temporal bones from patients in all age groups.

In two specimens, dye materials of different colours had been separately injected, one via the subarcuate artery, the other via branches of the internal auditory artery (group IX, chapter VI); the dye materials were seen to penetrate into one and the same vascular segment, still escaping passage through the capillary system.

Furthermore, if a dye material of one colour was injected into basilar artery vessels in one specimen already removed from the body, and a dye material of a different colour later was injected into the inferior petrosal sinus, arterio-venous shunts of arteriolar calibre would be observed (group X, chapter VI).

Thus, experimental vascular injections of this type made it possible to obtain an impression of a profuse vascular system in which flow between extra- and intracranial vessels was unobstructed; the same applies to flows between arteries and venous sinuses in the petrosal part, namely via anastomoses of arteriolar calibre.

Re Item C.

Since the above mentioned vascular plexus in the otic capsule apparently is well suited for injections to be applied to temporal bones from patients in all age groups, it was possible to demonstrate a vascular intercommunication between intralabyrinthine vessels and vessels in the otic capsule, even further to the lumen in the carotid canal and the vascular system of the promontory of the middle ear, in analogy with features described in chapter VII.

The latter type of anastomoses could be followed in 16 specimens, all of which were well-filled with contrast media. In five of these specimens, one single, thick, cleared section proved sufficient for the tracing of the vascular anastomoses from the basal cochlear coil, via the "vascular key area" to the vascular network of the promontorium. Besides, in one of these specimens, vessels emerging from radiating arterioles and extending directly to the vascular system of the middle ear were also demonstrable. In other words, anastomosing vessels can be traced

the "Cozzolino zone" and the degree of filling throughout the remaining part of the otic capsule The table is identical with table 1 in treatise F The term "vascular key area has substituted that of "Cozzolino s zone" because the vascular supply in this area is known to be particularly rich in the present study it includes the osseous separation between the basal and middle coils in other words, the area in which anastomoses between the cochlea and the otic capsule were found to be most abundant (chapter VII)

Table 3

		Degree of filling within the vascular key area as compared with filling in other parts of the capsule			Total
		Optimum	Equal	Poor	
Degree of filling in a.i.c.a. ( ) branches	Via internal auditory artery optimum	13	5	0	18
	Via subarcuate artery· optimum	1	not filled 3		6
	Degree of filling: equal	4	5	0	9
Injections into branches of the carotid artery exclusively		1	1	0	
Two injections. (1) via the carotid artery (?) via branches of a.i.c.a. (*)		4	0	0	4
Total		23	14		39

( ) anterior inferior cerebellar artery

The degree of filling within the various areas of the otic capsule.

Among the temporal bones those derived from old patients were found to be best filled even though the latter might have been suffering from generalized arteriosclerosis. Thus in the present series, the degree of filling of vessels in the otic capsule seemed to be independent of the age of the individuals.

In excess of the 'vascular key area" the area surrounding the vestibular semicircular canals appeared to be especially well filled the latter applies in particular to specimens filled via the subarcuate artery

Hence certain areas of the otic capsule were found to be particularly easy to fill by injection of contrast medium

Re item B

In 13 well-filled specimens into which one dye material had been injected via the anterior inferior cerebellar artery vessels could be traced throughout their course from the subarcuate artery to the promontory of the middle ear In these specimens

in temporal bones from senile patients and in bones from much younger individuals. These authors held also that the rate of metabolism in bone structures in temporal bones ranged at a level higher than that in any other bone in the body

The ratio of blood volumes in the otic capsule to volumes in the membraneous labyrinth was studied in guinea pigs by *Morizono* (1968) Radioactive chrome (Cr^{51}) served as tracer Accordingly 85 % of the blood volume in temporal bones was found to be localized to the osseous capsule while no more than 15 % was localized to intralabyrinthine sites.

Many of the previously published experiments as well as the results obtained by the author of these presents seem to indicate that the otic capsule is composed of bone which is particularly well-provided with vessels and in which the rate of metabolism is high, even in very old patients.

The conclusion to be drawn is therefore that possibilities of additional and considerable vascular supplies to the membraneous parts of the labyrinth, via the otic capsule are in evidence in all individuals no matter their age

from the membraneous cochlea to the middle ear via two or three layers of the otic capsule (namely: the endosteal layer the enchondral layer and the periosteal layer) As to the last mentioned *the periosteal layer the course of vessels through* this could be seen to proceed via the so-called "periosteal pins" i e. vessels running perpendicular to the surface of the promontory of the middle ear until they join the vascular system in the enchondral layer

In two specimens into which differently coloured dye materials were applied into extra as well as intra-cranial vessels (one specimen from group VI and one from group VII chapter VI) contrast media of either colour were found to appear in all layers *of the otic capsule as well as in all cochlear structures, includ*ing the modiolus, the basilar membrane and the lateral membraneous cochlear structures the same applies to all cochlear coils. In addition, the contrast medium injected via the carotid artery was found to invade the vascular system of the membraneous labyrinth via the otic capsule most profusely via the "vascular key area The same phenomenon was encountered in two control specimens into which the media had been injected exclusively via the common carotid artery (groups IV and V chapter VI)

Discussion and conclusion

In excess of the anastomoses in the otic capsule and those between the otic capsule *and the membraneous labyrinth demonstrated by means of injections using* granular media or alkaline phosphatase reagents numerous other vessels of these types were visualized by means of staining with osmic acid

In perfectly filled specimens, even in some originating from old patients suffering from generalized arteriosclerosis, the vascular capacity via vessels in the internal auditory canal seemed equal to that of all demonstrable anastomoses between the cochlea, directly through the various layers of the otic capsule and into remote vascular areas *Hence the demonstrable vascular supply via the otic capsule is apparently of value for the cochlear nutrition,* it may even be of value for its structural integrity whenever the blood supply to cochleae via vessels through the internal auditory canal is compromised

The vascularity *per se* in the osseous substance of the otic capsule has been an object of discussion in the literature

According to some authors, e g. *Rius and Mendoza* (1961) *Sercer and Krmpotić (1966) and Mendoza and Rius (1967) this vascularization was rather poor even insufficient and might be responsible for a development of necrotic bone* processes to be encountered in all patients, no matter their age

Against this argues the fact that *Gussen* (1968) by means of celloidine sections and conventional staining methods, found the otic capsule to be a site of a vivid bone construction and decomposition throughout life The latter finding has been verified by *Zechner and Altmann* (1969) who studied the enzymatic activity of the *same structures in temporal bones from patients in different age groups* They observed that concentrations of acid mucopolysaccharides were almost identical

sels were in all cases filled with "Microphil" or with a grained dye material suspended in 10 / gelatine. In the remaining 10 cases, vessels in the acoustic nerves were either insufficiently filled (six out of the 10) or they had been reproduced by staining of the vascular walls, using alkaline phosphatase reagent (four out of the 10). It proved impossible to judge the pattern on the basis of freeze-sections of the acoustic nerve and consequently these specimens are not included in the final survey.

In 24 out of the 33 specimens studied, injections managed to fill the Schwann part as well as the glial part of nerves. Filling was optimum in the Schwann part in all cases. In the remaining nine specimens, satisfactory filling was obtained only in one of the two parts. In two out of these 24 specimens, two dye materials were used for the reproduction of the intraneural vessels: they were injected via the anterior inferior cerebellar branches and carotid branches respectively. Both dye materials coincided in one and the same vascular segment within all zones of these nerves.

Dye materials injected via anterior inferior cerebellar branches were seen to penetrate into the intraneural branches, either via branches arising from this main stem or via branches from the internal auditory arteries: finally filling via vessels which united the dura in the internal auditory canal with the epineurium also was achieved.

The vascular pattern, calibres of vessels, and vascular density in the Schwann part seemed to be uniform, no matter the age of patients. The pattern might appear in the form of rectangular loops composed of longitudinal vessels of arteriolar calibre, or pre-capillary calibre: they were also seen to be composed of the interspersed transverse vessels. If counted over the diameter of nerves, an average of 15 to 20 such "meshes" would be in evidence.

The vascular density is considered to be identical at axial sites and at the more superficial sites in the Schwann part, no matter the age of patients. The nerve arises from the modiolus, emerging through tractus spiralis foraminosus, at which site an apparently high number of vessels is seen to enter into and emerge from the basal coil superficially in the nerve: this was true even in specimens *originating* from old patients with generalized arteriosclerosis.

In the glial parts of nerves, i.e. in the transitional zone as well as in more centrally situated zones, nothing but longitudinal vessels were in evidence as it had proved impossible to apply injections into transverse vessels. Such longitudinal vessels are often direct continuations of those in the Schwann part.

Two nerves belonging in this series, i.e. those in which filling of the vascular system was optimum, were re-embedded in celloidine and cut into serial sections measuring 7 micron: additional staining included haematoxylin-PAS. In similarity with findings in the thick, cleared sections, vascularization seemed to be most dense in the Schwann part. Furthermore, the vascular density at axial and peripheral sites seemed to be identical in all parts of the nerves.

Owing to the deficient filling in glial parts of the nerves it might be difficult to determine the ratio of numbers of vessels in patients in one age group to numbers of vessels in patients in other age groups.

CHAPTER IX

The Vascular Supply in Various Parts of the Cochlear Nerve

The cochlear nerve like other nerves consists of a Schwann part and a glial part.

Němček et al (1969) have reviewed the relevant literature on the histological histochemical and ultrastructural appearance of the cranial nerves In addition, they have submitted the results obtained in studies focused mainly on the "transitional zone" i e a narrow zone of the glial part of the nerve adjacent to the Schwann part. This monograph shall be briefly outlined

The nerve was found to be thickest peripherally in the Schwann part in which the supporting cells are Schwann s cells and vascularization is strikingly more abundant than in the glial part.

The glial part of the nerve consists of two parts, namely the so-called transitional zone and a more centrally situated glial zone Supporting cells in the transitional zone represent a variation of the oligodendroglial cells in the central nervous system they are of the so-called Hortega IV type, the external shape of which may remind of that of Schwann s cells their internal structure being identical with that of oligodendroglial cells Accordingly these cells are termed schwannoid cells" The rate of metabolism in the transitional zone is higher than rates otherwise observed in the nerve not infrequently it has been considered an element in the so-called glial barrier" surrounding the central nervous system The supporting cells at more central sites of the glial nerve are oligodendroglial cells as regards their structure it does not deviate much from that of supporting cells otherwise encountered in the white matter of the central nervous system

Takahashi (1966) compared the degenerative changes in the Schwann part of a cranial nerve (the vagus nerve) with changes in identical parts of nerves in the sympathetic nervous system and in one nerve in the extremities (the sciatic nerve) In specimens obtained from patients with severe generalized arteriosclerosis, the peripheral nerve was found to be a site of severe pathological changes whereas changes were moderate in the Schwann part of the sympathetic nerves and in the vagus nerve

The arteriosclerotic lesions in extra-cranial nerves have been described in greater detail, for instance by *Cottrell* (1940) *Eames and Lange* (1967) and *Ochoa and Mair* (1969)

Author's studies and results

In 33 temporal bones out of 43 intraneural vessels of the vestibulo-cochlear nerve were filled to a degree sufficient to allow a judgement of the vascular pattern Ves

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Owing to the deficient filling in glial parts of the nerves it might be difficult to determine the ratio of numbers of vessels in patients in one age group to numbers of vessels in patients in other age groups.

At the line of demarcation between the Schwann part and the glial zone of transition the vascular pattern changed abruptly from the type observed in the Schwann part into that seen in the glial parts This feature was observed in nerves from patients in all age groups

Discussion and conclusion

The vascular density throughout the Schwann part of the 8th cerebral nerve was found to be uniform in all specimens, no matter the age of patients. This is in conformity with the findings obtained by *Takahashi* (1966) in a study of the vagus nerve and the sympathetic nerves

The apparently large number of vessels to pass through that part of tractus spiralis foraminosus which leads to structures in the basal cochlear coil is not commensurate with data submitted by *Krmpotić* (1969) who declared that the foramina in tractus spiralis foraminosus would occlude late in life according to this author a strangulation of vessels and nerves entering into the structures of the basal cochlear coil might thus be one of the factors responsible for the development of presbycousis

The abrupt shifting from the dense and regular vascular patterns in the Schwann part to the less dense pattern or rather a vascular system into which injection had been more sparse seen in the transitional zone and other zones in the glial nerve, is in agreement with findings obtained by *Němeček et al* (1969)

As regards the severity of the degenerative changes, it should be mentioned that a similar abrupt shifting at the line of demarcation between the Schwann part and the glial part of the 8th cranial nerve has been observed in patients with generalized arteriosclerosis involving the main ramifications of the anterior inferior cerebellar artery in the internal auditory canal (patients in group I chapter IV) in these patients the lesions involving the Schwann part were found to range between mild and moderate degrees whereas changes in the glial parts of the nerve were considered to be severe even monstrous (approximately like those observed in the white matter of the cerebral hemispheres) (*Hansen and Reske-Nielsen* 1965)

CHAPTER X

Summary and Discussion of Clinical and Anatomical Findings

The clinical findings together with the patho-anatomical and normo-anatomical studies are summed up and discussed in chapter X. The object of the study has been to illustrate, even to define if possible, the aetiology involved in certain types of perceptive hearing loss, particularly that to develop late in life.

Re Part I

Temporal bones and brains from 14 patients have been exposed to microscopic study the histological findings have tentatively been correlated with those obtained by clinical and otological examination as well as by pure-tone audiometry

Examination of the patient discussed in chapter II (abstract of treatise A. Cortical Hearing Loss in a Patient with Glioblastoma) shows that the hearing capacity may vary parallel with cerebral lesions exclusively in the present case, oedema has been found to involve the cerebral hemispheres moreover the loss of hearing is found to be of the presbycousis type.

Chapter IV is an abstract of treatise B Pathological Studies in Presbycousis. Cochlear and Central Findings in 12 Aged Patients. The following conclusion is drawn. In 11 of the patients, the loss of hearing applies to the high-frequency range as well as to the low-frequency range the loss of hearing of tones in the high-frequency range seems to be attributable to lesions involving central as well as peripheral sites while the loss of hearing of tones in the low-frequency range seems to be due to lesions at cerebral sites exclusively the apical and middle coils remaining intact in the latter cases or the pathological changes might be slight only Among these 11 patients, the one in group IV is included though the lesion applies only to the right ear The hearing loss of classic presbycousis type in one patient (group III) is explicable only as a consequence of changes affecting the acoustic nerves and the brain since the cochlea is found to remain normal in this patient.

In chapter V (abstract of treatise C. Pathological Studies in Perceptive Deafness. A Patient with Hydrops of the Labyrinth) a patient is discussed in whom Ménière's disease arteriosclerosis, and loss of hearing of tones of all frequencies are diagnosed The hearing loss may have been due to pathological processes at peripheral as well as central sites.

Distribution of the pathological processes involving the cochlea and the cerebrum varies greatly from patient to patient, this seems particularly notable in the cases of patients suffering from presbycousis in whom the cochlear structures remain either intact or slightly to moderately altered as compared with the often severe

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tions to four vascular branches are established, namely to the spiral modiolar artery to the cochlear branch of the vestibulo-cochlear artery to intraneural vessels of the auditory nerve, as well as to vessels to and from the enchondral layer of the otic capsule At apical sites of the modiolus, however vascular communication is in evidence only to the spiral modiolar artery and the intraneural vessels of the auditory nerve

The abundant injections into the basal coil include also the vascular system of the basilar membrane even the vessel of the basilar membrane This feature is observed also in temporal bones derived from old patients in whom osmic acid staining of the organ of Corti discloses a coincident disappearance of hair cells there. In one such specimen it is even possible to trace grained contrast media between vessels in the basilar membrane and the vascular stria via vascular communications within Reissner's membrane at the site of the basal coil.

The further course of the vascular anastomoses through the other structures of the temporal bone is discussed in chapter VIII (abstract of treatise F Vascular Anatomy of the Human Temporal Bone. II. Vascular Anastomoses inside the Labyrinthine Capsule). It is attempted to have vessels in the otic capsule filled via basilar vessels (41 specimens) carotid vessels (10 specimens), and via both in one and the same temporal bone (8 specimens) The degrees of filling vary although variations are not dependent on ages of patients or types of grained contrast media applied

By means of such injections it is possible in 16 specimens to follow vessels in their courses between the internal ear and the middle ear throughout two or three layers of the otic capsule In addition, direct communication between carotid vessels and basilar artery branches might be demonstrable by injections into either one of these areas or into both within one and the same temporal bone In two cases, such communications are demonstrable within the cochlea where the dye materials appear in one and the same intracochlear vessel which might be one in the modiolus, in the basilar membrane, or in the vascular stria. Double-injections of this type also disclose anastomoses between separate anterior inferior cerebellar branches (the subarcuate artery and the internal auditory artery) in the bone substance *per se* Arterio-venous anastomoses of arteriolar calibre are also found to unite the inferior petrosal sinus with the arterial system. Such arterio-venous anastomoses of smaller calibres are seen to unite the vascular area of the subarcuate artery with the superior petrosal sinus

Certain areas of the osseous labyrinthine capsule which during foetal life are the sites of the most abundant penetration by connective tissue and vessels are seen to be particularly well filled with dye materials these areas are the following: the area round about the semicircular canals, particularly well-filled via the subarcuate artery branches the area between the base of the cochlea (including the osseous shelf wedged in between the middle and the basal coil), the vestibule, the fundus of the internal auditory canal, and the middle ear promontorium, particularly well-filled via the internal auditory artery branches The latter area is termed "the vascular key area by the present author while the same region is termed Corzolino's zone according to *Eckert-Möbius* (1926)

cerebral lesions Intracranial vascular changes including those involving the basilar circulation and vessels in the internal auditory canal seem also to be extremely severe while structures in the peripheral auditory organ are well preserved

Inspired by the results thus obtained, the author embarked upon an experimental study of vessels in order to examine whether the relative integrity of intralabyrinthine structures might be maintained by hitherto unrecognized vessels in excess of the branches of the intracranial vascular system

Re Part 2

In 43 temporal bones obtained from 33 individuals, the vascular system has been filled to various degrees by means of a micro-injection method elaborated by the author The *composition of the material is very heterogeneous both as regards the* distribution according to age of patients and the media used for injections also the sites of injections vary the media being applied either via extra or intra-cranial vessels The techniques used for injection and dissection are described in detail in chapter VI (the description of the method used for injection is an abstract of that previously published in treatise D *Vascular Anatomy of the Human Temporal* Bone A Preliminary Report)

Coincident microscopy of the equivalent brains and injections into these have not been possible Gross inspection of brains from these old patients, however might often disclose severe, mostly sporadic vascular changes. Severe arteriosclerotic changes were also seen to involve the basilar vessels. Intracranial vessels supplying right and left temporal bones were found to deviate greatly in calibres and morphology

In chapter VII (abstract of treatise E. Vascular Anatomy of the Human Temporal Bone I Anastomoses between the Membraneous Labyrinth and its Bony Capsule) the vascular communication between the cochlea and the otic capsule is described such communications are filled with the above mentioned contrast media. In all temporal bones where the contrast media are seen to penetrate to the loosely built bone shelf between the basal and middle cochlear *coils (31 bones),* vascular anastomoses of arteriolar calibre are found to unite the modiolus with the vascular system in the enchondral layer of the otic capsule This feature is demonstrable whether injections are applied via basilar vessels or carotid branches Furthermore vessels of calibres paralleling those of *radiating arterioles of the vestibular scale are demonstrable in 15 specimens* these vessels arise at right angles to the latter and transversing the endosteal layer they unite with the vascular system of the enchondral layer The phenomenon is seen in all of the cochlear coils Moreover in 14 specimens the contrast media are seen to penetrate between fibrils of the endosteal layer

By this means it is demonstrated that *the cochlear vessels are no end-arteries* Vascular communication between the otic capsule and the intracochlear structures is apparently especially abundant at the level of the basal coil including the vascular network *around its spiral ganglion. In this cochlear region* communica

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The hearing loss applying to the low-frequency range is in five patients found to exceed the level otherwise encountered in cases of presbycousis (three patients in group I, one in group IV (cf table 1)) the fifth patient who is discussed in chapter V was suffering from Ménière's disease. It is rather difficult to decide whether a parallel can be drawn between the degree of the loss of hearing of tones in the low-frequency range and the severity of the pathological processes involving any specific site in the cerebral auditory pathways and centres. It is concluded, however that such loss of hearing of tones in the low-frequency range mainly if not exclusively may be attributable to cerebral lesions in these senile patients (cf. chapter IV) in whom nothing but insignificant degenerative lesions are seen to involve structures of the middle and apical coils, even though degrees of such deafness may vary considerably As regards the patient with Ménière's disease (chapter V), the histological findings suggest that the hearing loss applying to the low-frequency range might be attributable in part to the cerebral lesions

Other investigators, for instance *Jørgensen* (1961) and *Ishii* (1967) have also observed such heterogeneous distribution of arteriosclerotic, vascular degenerative changes including the involvement of intracranial vessels and vessels in the internal auditory canal in cases in which the cochlear vessels are only moderately affected

On the other hand, the degrees of degenerative changes in cochlear as well as cerebral neural elements have not been described before A few authors, namely *Metzker* (1958) and *Kirikae* (1964) observed disappearance and degeneration of cells in the auditory pathways and centres of the brain stem.

In some of the patients discussed in Part 1 a distinct line of demarcation was seen to distinguish between the severe, even monstrous, changes involving the central neural elements and the moderate changes at peripheral sites, namely at the site of transition from the glial part to the Schwann part of the acoustic nerve within the internal auditory canal *Takahashi* (1966) observed similar features in the intracranial nerves of patients with severe generalized arteriosclerosis. Morphological studies by *Němeček et al* (1969) disclosed an equally distinct line of demarcation at the identical site in the 1st neurone of the auditory pathways in addition, these authors found that vascularization pertaining to the peripheral Schwann part was strikingly richer than that in the glial part of the 8th nerve

On the basis of the experimental injections described in Part 2, the author estimates that the vascular pattern is most dense within the Schwann part of the acoustic nerve this applies even to findings in old patients.

Likewise it emerged that the cochlea is in vascular communication with the surrounding bone structures and, in fact, is not isolated from the latter The intracochlear structures in all coils, but mainly those in basal coils, are actually in vascular communication with extracranial areas via anastomoses of arteriolar calibre The latter is demonstrated by injections via intra- and extra-cranial vessels as well as by coincident injections via both into temporal bones from patients in all age groups.

The fact that intracochlear structures remain well preserved even in patients



Finally the vascular pattern in the vestibulo-cochlear nerve is studied in this series of temporal bones to which injections are applied The study is described in chapter IX (abstract of treatise F Vascular Anatomy of the Human Temporal Bone III The Vascularization of the Vestibulo-Cochlear Nerve) In the peripheral part, the Schwann part, of the nerve (the term referring to the presence of Schwann s supporting cells) the vascular pattern is found to be perfectly normal in patients in all age groups

The vascular pattern is seen to change distinctly at the site of transition between the Schwann part and the glial parts of the nerve (termed according to the different types of supporting cells involved) Vascularization seems to be less rich in the glial than in the Schwann part. The same is noticed in two well filled nerves cut into serial sections of a thickness of 7 micron and stained with haematoxylin-PAS The vascular density in peripheral and axial parts of the nerves is apparently equal

Discussion

The cited literature and the most essential results obtained in the present study have formed the basis of a discussion of the aetiology involved in perceptive deafness diagnosed in the patients comprised in the author's series

It is attempted to evaluate and compare degrees of severity of the pathological processes involving the temporal bones and brains of the patients discussed in Part 1 The findings obtained suggest that the loss of hearing is attributable mainly to the cerebral lesions.

In patients in whom the degree of deafness of the presbycousis type "pertaining to age" the most severe lesions are found to involve the white matter of the cerebral hemispheres together with the glial part of the acoustic nerve (three patients in group I one in group II chapter IV (table 1 page 28))

In two cases the hearing losses are of degrees beyond that "pertaining to age" while the audiometric curves are found to be of the typical presbycousis shape In one of these patients in whom the peripheral auditory organ is intact, the most severe pathological processes involve the cerebral hemispheres (cf chapter II the data are obtained during periods when involvement of both cerebral hemispheres is manifest in the patient concerned) lesions in the other patient (group II chapter IV (cf table 1)) are found to involve the cerebral hemispheres and the acoustic nerves while the cochlea are seen to remain intact.

The loss of hearing applying to the high-frequency range is in three patients found to exceed the level otherwise encountered in cases of presbycousis (two patients in group I one in group II chapter IV (cf table 1)) The cerebral lesions are in all cases considered to be much more severe than those observed in the peripheral auditory organs Besides the cochlear changes are found to be of the same degree as those observed in cases where curves suggest presbycousis Thus the hearing loss applying to the high-frequency range and exceeding that otherwise considered typical of old age is assumed to be attributable mainly to the cerebral lesions

that this feature is demonstrable in temporal bones from patients in all age groups, it seems rather paradoxical that the ganglion cells in the basal coil are the ones which are prone to disappear and degenerate. One reason may be that metabolic waste products might accumulate mainly at this site where the blood supply is most profuse; the latter postulation is substantiated by the fact that hearing losses in old individuals are found to be attributable to nutritional factors (*Rosen and Olin*, 1965). Another explanation is suggested by *Meyer zum Gottesberge et al.* (1965) and *Rauch* (1967) according to whom the energy consumption is highest in the basal cochlear coil where also wear and tear is most marked, as demonstrated by *von Békésy* (1960) who observed that all tones would produce vibrations in the basal cochlear coil whereas the apical cochlear coils are activated exclusively by tones in the low-frequency range.

It remains open to discussion whether lesions of ganglion cells in the basal cochlear coil are contributory to the hearing losses observed in patients in the various series; in fact, *Crowe et al.* (1934), *Schuknecht* (1955) and *Citron et al.* (1963) declared that the hearing capacity may remain intact even though 50–80 % of the ganglion cells are destroyed. It should finally be emphasized again that the hearing loss of the presbycousis type diagnosed in one patient (chapter II) seems to be attributable almost exclusively to pathological processes involving the cerebral hemispheres.

The lesions in the organ of Corti (Part 1) are probably artefacts which may have developed after death. In the present study similar lesions were demonstrable in osmic acid stained preparations from old individuals (cf. Part 2); such staining served to reveal the disappearance of hair cells at the site of the basal coil; this feature is in conformity with findings obtained by *Bredberg* (1968). Furthermore, coincident injections of dye material into these specimens are seen to fill vessels in close connection with the organ of Corti, even in the region of the basal coil (Part 2, chapter VII). This is in conformity with findings obtained by *Axelsson and Ernstson* (1970) in experiments with waltzing guinea pigs in which injections were applied into the vessel of the basilar membrane.

So far it cannot be decided whether the demonstrated lesions in the organ of Corti may have contributed to the loss of hearing in the patients here discussed; in fact, the histological findings may not have been of any consequence. *Ruben* (1963) found the cochlear microphonic potential to be normal in an old patient with presbycousis. Also *Schneider and Jaeger (1969)* who exposed guinea pigs to histochemical analysis and, in addition, measured the cochlear microphonic potential as a standard of the degenerative changes to develop in the organ of Corti, found such functional measurement out of proportion to the histologically demonstrable changes induced by "white noise".

All cochlear vessels in the patients discussed in Part 1 seem to remain relatively well-preserved; also temporal bone vessels from the same sites (discussed in Part 2) are suitable for injection, no matter the age of patients.

with severe arteriosclerosis may find its explanation in this additional vascular supply to the cochlea. This opinion is formed on the basis of aa pooling of vessels into which grained contrast media is applied and of vessels reproduced by means of osmic acid perfusion Such additional supply serves also to explain why degeneration in the right and left cochleae is symmetrical in patients with presbycousis, irrespective of the marked asymmetry of vessels at the base of the brain and the uneven distribution of arteriosclerotic plaques in this vascular region The asymmetry of vessels in the basilar system has been demonstrated by *Levin* (1964) and by the present author (chapter VI)

This additional vascular supply to the cochlea suggests that bone anastomoses are of value for the nutrition of the cochlea, even in very old individuals, because the apparently dense vascular network in temporal bones from the latter are satisfactorily filled *Owing to the heterogeneity of the material as regards media* used for injections, sites to which injections are applied, and also the varying degrees of filling in vessels in patients in the individual age groups, it is hardly possible to draw any conclusions concerning the number of vessels which, in patients in the individual age groups, may be suitable for injection

It appears from the literature however that the rate of metabolism in bone structures of the temporal bone remains almost unchanged throughout life (*Zechner and Altmann* 1969) and also that the vascular supply is only moderately affected by arteriosclerosis in old patients (*Gusten* 1968) Even so the latter author found thrombi to be numerous in vessels in individuals in whom the severity of generalized arteriosclerosis measured by their age, was abnormal (*Gusten* 1969)

The intracochlear changes observed in the patients discussed in Part 1 are manifest mainly in the form of varying degrees of disappearance and degeneration of ganglion cells at the level of the basal cochlear coil. Any proportionality between *degrees of these pathological changes and hearing losses diagnosed is not demon*strable In patients with presbycousis for instance apparently normal conditions (patient no 6 chapter IV) may alternate with a disappearance of about 75 % of the cells in other pat ents. In two patients whose hearing losses of the presbycousis type are of a severity otherwise observed in much older patients conditions seem to be normal (patient no 11 group III chapter IV and the patient discussed in chapter II whose hearing impairment occurred during periods when bilateral hemispherical changes were manifest)

This discrepancy between degrees of severity of the pathological processes and the diagnosed hearing losses has been described also by *Crowe et al* (1934) *Saxén* (1952) *Fleischer* (1956) and *Jørgensen* (1961)

By means of the vascular injections described in Part 2 *it is possible to demonstrate that vessels communicating with the capillary plexus surrounding the spiral cochlear ganglion are most numerous at the site of the basal coil* Vessels in direct communication with the otic capsule (chapter VII) and further progressing to extracranial areas belong to this category (chapter VIII) Taking into consideration

that this feature is demonstrable in temporal bones from patients in all age groups, it seems rather paradoxical that the ganglion cells in the basal coil are the ones which are prone to disappear and degenerate. One reason may be that metabolic waste products might accumulate mainly at this site where the blood supply is most profuse; the latter postulation is substantiated by the fact that hearing losses in old individuals are found to be attributable to nutritional factors (*Rosen and Olin* 1965). Another explanation is suggested by *Meyer zum Gottesberge et al.* (1965) and *Rauch* (1967) according to whom the energy consumption is highest in the basal cochlear coil where also wear and tear is most marked, as demonstrated by *von Békésy* (1960) who observed that all tones would produce vibrations in the basal cochlear coil whereas the apical cochlear coils are activated exclusively by tones in the low-frequency range.

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All cochlear vessels in the patients discussed in Part 1 seem to remain relatively well-preserved; also temporal bone vessels from the same sites (discussed in Part 2) are suitable for injection, no matter the age of patients.

Furthermore the injection experiments provide evidence of a vascular communication between the vascular stria and the basilar membrane namely via Reissner s membrane

Atrophy of the vascular stria like that observed by *Schuknecht* (1955) and *Ishii* (1967) in senile patients is not encountered in any of the patients discussed in Part 1 Indeed, the vascular stria is found to be well-filled in temporal bones removed from old patients (Part 2)

Conclusion

According to the histological analysis of structures in temporal bones and brains in patients with various types of perceptive hearing impairments, such impairments as apply to the high frequency range seem to be attributable, at least partly to lesions involving cerebral sites whereas impairments applying to the low frequency range apparently are due to cerebral lesions exclusively Only the patient with Ménière s disease represents an exception

Examinations of temporal bones to which contrast media are applied seem to substantiate the hypothesis according to which arteries in the peripheral auditory organ are not end-arteries In fact, it applies to individuals in alle age groups that the cochlear vessels are found to communicate with intracranial as well as extra cranial sources The latter feature may explain why structures of the internal ear are found to be relatively well preserved in elderly patients (Part 1) in spite of the severe neurogenic and vascular anomalies encountered at the more centrally localized sites in the auditory pathways

As regards the intracochlear structures it must be admitted that there is a certain discrepancy between the particularly rich vascular supply to the basal cochlear coil and the rather severe degenerative lesions to develop within the same region As to the vascular supply to the middle cochlear scale, it should be stressed that grained contrast media are seen to penetrate right into the vessel of the basilar membrane vessels being well filled even in areas where coincident disappearance of hair cells in the organ of Corti is in evidence Furthermore these vascular injections serve to demonstrate the vascular communication between the basilar membrane and the vascular stria, via Reissner's membrane

Thus by way of a comparison of findings in ears and brains (Part 1) and by means of experimental injections into vessels of the temporal bone (Part 2) perceptive hearing impairments including the so-called "hearing loss pertaining to age is found to be mainly attributable to the pathological processes at intracranial sites

Continued research in the fields of audiology and pathology including studies of all parts of the complicated auditory system, is urgently required Such research should include examination of all structures within the temporal bones, including the otic capsule In this connection the attention shall be directed to the technique used for such injections, a technique which has been improved and elaborated by

the author this technique is combined with the generally accepted methods hitherto used in phase-contrast microscopy and in routine histological procedures. It is recommended to use thick, cleared sections, as described in the present study including cutting into thinner sections and additional staining according to conventional histological methods.

The technique may prove valuable whenever specific problems are to be solved, for instance, problems involved in a definition of the factors responsible for the acutely developing hearing losses. On the assumption that the vascular anastomoses here described contribute to the preservation of a certain integrity of structures in the internal ear in patients of this category it may be taken into consideration to institute oto-neurosurgical measures by which to counteract the defect. Moreover comparative studies of temporal bones and cerebral structures in patients exposed to several audiological tests seem to be of importance for the establishment of more advanced neuro-otological diagnostics.

SUMMARY

In the present monograph including clinical examinations and studies of the normal anatomy as well as the patho-anatomical features involved, it is attempted to detect the factors responsible for the development of the various types of perceptive hearing loss in particular those responsible for the development of deafness termed "hearing loss pertaining to age"

The monograph comprises two parts

Part 1 Histological studies of temporal bones and brains from patients with diagnosed hearing loss of perception type (chapters I–V)

Part 2 Experiments including injection of contrast media into the vascular system in temporal bones from man (chapters VI–X)

Chapter I The material is described and the methods used for dissection of specimens and histological staining of temporal bones and brains are discussed

Chapter II The lesions observed in a 43-year-old patient are discussed His hearing was found to be normal but a glioblastoma was seen to involve one cerebral hemisphere Audiometry performed twice during two periods in which cerebral oedema, provoked by the surgical treatment of the tumour was manifest, revealed on both occasions a symmetrical loss of hearing applying mainly to tones in the high frequency range on both occasions, audition paralleled that which according to the literature otherwise is seen in normal 75 year-old patients The last episode of cerebral oedema terminated in the sudden death of the patient On the basis of histopathological analysis of the brain and of the apparently normal left temporal bone the following conclusion is drawn Throughout the periods in which the pathological changes provoked by the tumour involved exclusively the right cerebral hemisphere and the right side of the brain stem, with the exception of the trapezoid body audition remained normal in this patient while a hearing loss of the presbycousis type occurred during the two episodes of surgically excited cerebral oedema these episodes were associated with *extinct action of the left cerebral hemisphere* In other words, audition is found to fluctuate parallel with pathological lesions involving the cerebrum

Chapter III comprises a review of previously published works in which the hearing capacity of senile patients is collated with findings obtained by histological studies of isolated parts of the auditory pathways for instance, single sites in the temporal bone or in the brain

Some authors have studied the peripheral auditory organ and concluded that pathological lesions at that site were not sufficient to explain the development of the diagnosed hearing loss consequently they suggested that cerebral lesions might be responsible in part, particularly in cases in which the hearing loss applied to tones in the low-frequency range

The attention is directed also *to* a few reports according to which degeneration of the acoustic nuclei in the brain stem had been demonstrable

Studies are not available however in which the peripheral as well as the cerebral neurones have been examined in patients whose hearing loss developed late in life

Chapter IV The series discussed comprises 1_ senile patients who all except one were above the age of 65 years The cerebral auditory pathways, the auditory nuclei in brain stem and cerebral hemispheres, as well as the right and left temporal bones were studied in these patients. In one patient, examination applies only to the right ear

In 11 of the patients, the hearing loss of tones in the high-frequency range is apparently due to cerebral as well as peripheral lesions the loss of hearing of tones in the low-frequency range seems to be attributable exclusively to cerebral lesions since the apical and middle coils remain normal, or only slightly damaged. In one of those 11 patients (the one in group IV) only the right-sided hearing loss could be explained, as mentioned above. In one patient (the one in group III), the loss of hearing of tones in the high-frequency range is explicable exclusively as a consequence of the lesions involving the acoustic nerve and the brain stem since the cochleae on either side remain of normal appearance

Chapter V The past medical history of an 83-year-old patient with Ménière's disease is reviewed. The pathological changes involving the temporal bones and the brain are discussed

The bilateral labyrinthine hydrops can hardly be held solely responsible *for the* hearing loss in particular it cannot be held responsible for her hearing loss applying to tones in the low-frequency range taking into consideration that the labyrinthine hydrops involved mainly the *right* ear on which audition was best preserved Furthermore, the lesions involving the *1st* neurone in the acoustic pathways, mostly lesions apically in the cochlea, are not sufficient to explain a loss of hearing of tones in any range on the *other hand*, disappearance and degeneration of cells are by far more marked in the acoustic nuclei and auditory pathways in the brain and hence, the hearing impairment must be considered attributable to cerebral as well as to peripheral lesions, whether the hearing loss applies to tones in the low or high-frequency range.

In contrast, the impairment of the vestibular function is apparently attributabl exclusively to cerebral lesions since there is a clear-cut discrepancy between the severely reduced caloric reactions in both ears and the normal aspect of the vestibular labyrinth, including the 1st neurone coincident with the extremely severe lesions of the vestibular nuclei and pathways in the brain stem.

SUMMARY

In the present monograph including clinical examinations and studies of the normal anatomy as well as the patho-anatomical features involved it is attempted to detect the factors responsible for the development of the various types of perceptive hearing loss, in particular those responsible for the development of deafness termed "hearing loss pertaining to age"

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which anterio-posteriorly separates the vestibule from the cochlea, including the osseous shelf between the basal and the middle coils and which medio-laterally separates the middle ear promontory from the internal auditory canal.

Throughout this vascular system, and in all layers of the otic capsule, it is possible to follow the unintermittent course of vessels of arteriolar calibre between the intracochlear structures and distant structures such as the promontory of the middle ear and the internal carotid artery in its course through the carotid canal.

Chapter IX The vascular supply to the acoustic nerve is described. It applies to all age groups that the vascular system in the Schwann part of nerves is richer and more regular than that in the glial parts In the internal auditory canal, the transition between the two patterns produced by injections is clear-cut.

Chapter X The subject matter of this chapter is a synoptic conclusion and discussion of the findings described in Parts 1 and 2.

Part I By means of the available methods for light microscopy the degenerative lesions of labyrinthine structures in 14 patients with various types of hearing losses, mainly of the presbycousis type, are found to be less marked than those involving cerebral auditory pathways and centres. In fact, in two patients with presbycousis, the peripheral hearing organ is apparently normal. The Schwann part of the acoustic nerve seems to be well-preserved despite the severe arteriosclerotic lesions of vessels passing through the internal auditory canal at extraneural sites conversely degeneration in the glial part of nerves is of a degree similar to that involving the white matter of the cerebral hemispheres. As regards the cochlea, the only pathological changes other than those attributable to autolysis, include disappearance and degeneration of ganglion cells at the site of the basal coil of the spiral ganglion, although it must be admitted that the feature is not proportional to the diagnosed loss of hearing of tones in the high-frequency range

Thus the conclusion must be that the factor or factors responsible *for the* diagnosed losses of hearing are such lesions as involve central as well as peripheral sites in the auditory system two of the patients in whom hearing *curves* were of presbycousis type represent the exception to this rule, their hearing losses being attributable to cerebral lesions exclusively

Part 2 The results obtained by experimental injections into vessels of 43 human temporal bones derived from patients in all age groups are submitted in part 2. The purpose of such injections is to provide an explanation of the above mentioned findings in temporal bones from the patients discussed in *Part 1*

It is demonstrated that the cochlear arteries are not end-arteries, rather they are seen to unite with vessels in the otic capsule, particularly at the site of the basal cochlear coil extending further to structures of the middle ear finally to unite directly with carotid branches. Accordingly *the* cochlea can be filled also via injections into carotid branches Such anastomoses are demonstrable in temporal bones no matter the age of individuals *from* whom they are removed, the otic capsule is also found to be well-filled with contrast *media*, even in specimens derived from old patients with severe, generalized arteriosclerosis The demon-

Chapter VI The composition of the material (discussed in Part 2) is described together with the methods used for removal of specimens, experimental injections, and dissection of the 43 temporal bones derived from patients in all age groups. On the basis of this material it is endeavoured to explain some of the patho-anatomical findings discussed in Part 1

Chapter VII is concerned with the vascular communication between the membraneous labyrinth and its otic capsule also the pattern of filling obtained in certain areas of the cochlear vascular system is described

In all temporal bones in which the contrast media appear at the site of the basal cochlear coil in the modiolar vessels (a total of 31) the media are seen to penetrate directly into the enchondral layer of the otic capsule namely via the osseous shelf separating the basal coil from the middle coil. Arterial as well as venous anastomoses between extra and intra labyrinthine vessels are in evidence. In addition vascular communications traversing the endosteal layer are found to unite the intracochlear vascular network with vessels of the enchondral layer This feature is demonstrable in all cochlear coils Such communication is mediated either via canaliculi of capillary calibres interspersed among the osseous fibrils in the endosteal layer *per se* or via arterioles arising from the radiating arterioles of the vestibular scale Anastomoses of these types are demonstrable in all temporal bones, no matter the age of individuals from whom they are derived In the present series they are encountered in one 5-day-old infant as well as in patients above the age of 90 years The various types of vascular anastomoses can all be filled by injections of contrast media via intra as well as extra-cranial vessels known to supply temporal bones Accordingly *the intralabyrinthine arteries are no end arteries*

The intracochlear vascular supply seems to be most abundant at the site of basilar coil structures, especially at the vascular network surrounding the spiral ganglion. Furthermore, vessels in the basilar membrane seem to be well-filled, irrespective of the severity of the degenerative changes involving the organ of Corti, visualized by staining with osmic acid Vessels uniting the vascular stria with the basilar membrane vessels via Reissner s membrane are also in evidence

Chapter VIII The vascular pattern of the otic capsule reproduced by injections into temporal bones, is described the specimens are the same as those discussed in chapter VII The enchondral layer seems to be especially well-provided with vessels this feature is apparent from the injection pattern in temporal bones from patients in all age groups This layer can be filled through extra as well as intra cranial arteries Injections via both sources in one and the same specimen disclose end to-end anastomoses of arteriolar calibres between these Furthermore such duplicate injections reveal the presence of arterio-venous anastomoses which also are of arteriolar calibres

As regards the osseous regions of the osseous capsule filling is most satisfactory in. (a) the region medially to the subarcuate fossa, mainly supplied from the intracranial vessels via the subarcuate arterial branches (b) the osseous region

RESUMÉ

I det forelagte arbejde er det forsøgt ved hjælp af kliniske undersøgelser og normal anatomiske såvel som pathologisk-anatomiske studier at undersøge årsagerne til forskellige former for perceptionshøretab – specielt det såkaldte »aldersbetingede« høretab.

Arbejdet er inddelt i 2 afsnit.

1. Histologiske studier af tindingeben og hjerner fra patienter med kendte perceptionshøretab (kapitel I–V).

2. Experimentelle kontraststofinjectioner af karsystemet i humane tindingeben (kapitel VI–X).

Kapitel I indeholder en beskrivelse af materialet og af de metoder der er brugt ved udtagning og farvning af det histologiske materiale omfattende tindingeben og hjerne.

Kapitel II En 43-årig patient med normal hørelse er fulgt audiometrisk i 2 perioder hvor hjerneødem optrådte efter operative indgreb mod tumor. I begge perioder fandtes symmetriske høretab specielt i højfrekvensområdet, svarende til hørelsen man, *ifølge* litteraturen, møder hos 75-årige patienter. Patienten døde pludseligt i tilslutning til sidste hjerneødemperiode. Ud fra en histopatologisk analyse af hjerne og af venstre os temporale, der findes normale, konkluderes følgende: I perioderne, hvor de patologiske forandringer forårsaget af tumor begrænser sig til h. cerebrale hemisfære og h. side af hjernestammen bortset fra corpus trapezoideum, er hørelsen normal. Under de to perioder med diffust *hjerneødem i forbindelse* med operationerne, hvor også venstre hemisfære delvis er sat ud af spillet, har patienten det presbyacusisåhgnende høretab. Det vil sige, at hørelsen fluctuerer med de skiftende patologiske tilstande i storhjernen.

Kapitel III omfatter en summarisk gennemgang af tidligere publicerede arbejder hvor forfatterne sammenholder hørelsen hos ældre patienter med de histologiske fund i eet enkelt afsnit af hørebanerne, *enten i os temporale eller i hjernen*.

Enkelte forfattere, der har undersøgt det *perifere* høreorgan konkluderer, at de patologiske forandringer her ikke er tilstrækkelige til at *forklare* de fundne høretab hvorfor cerebrale forandringer må have spillet en rolle, specielt for lavfrekvenshøretabenes vedkommende.

Desuden refereres et par meddelelser vedrørende undersøgelser af de akustiske kerner i hjernestammen, der *fandtes* degenererede.

I intet arbejde er såvel perifere som cerebrale neuroner undersøgt hos patienter med høretab opstået i senium.

strable blood supply via the otic capsule serves to explain the observation of well-preserved cochlear structures of the middle and apical coils in old patients. On the other hand these injections fail to explain why structures of the basal cochlear coil have degenerated taking into consideration that vascular anastomoses, via the otic capsule, to this part of the cochlea are found to be particularly abundant. Injections of contrast media fail to provide an explanation of the degenerative changes to be observed by means of osmic acid staining of the organ of Corti and seen to involve the basal cochlear coil in temporal bones from senile patients with generalized arteriosclerosis. In these cases the contrast media are seen to penetrate even into the vessel of the basilar membrane

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Kapitel IV Hos 12 senile patienter hvoraf kun een er under 65 år har man undersøgt cerebrale hørebaner og kerner i hjernestammen og hemisfærerne såvel som begge perifere høreorganer I eet tilfælde dog kun højresidige

Hos de 11 patienter (hos 1 patient (gruppe IV) var kun højre øre impliceret) hvis høretab omfattede både *høje* og *lave toner synes højttonetabet at være* central såvel som perifert betinget, mens lavtonetabet må være udelukkende centralt betinget idet de apicale og mellemste vindinger er normale eller kun let forandrede. Hos en enkelt patient (I gruppe III) kan høretabet, der er et højttonetab kun forklares som et resultat af *forandringerne i nervi acustici og hjernen idet* cochleae på begge sider er normale

Kapitel V Man gennemgår sygehistorie og patologiske fund i ossa temporalia og hjernen hos en 83 årig patient med morbus Ménièri og arteriosclerose

Den dobbeltsidige hydrops labyrinthii synes ikke at være eneste årsag til patientens *høretab* specielt ikke til det tab der omfatter lavfrekvensområdet, da den er mest udtalt i grad og udstrækning i højre øre, hvor hørelsen er bedst bevaret. Tillige er de patologiske forandringer i 1 neuron af de akustiske baner ikke tilstrækkelige specielt ikke de i den apicale del af cochlea, til at forklare en hørenedsættelse omfattende noget trin i frekvensområdet derimod er udfald og degeneration langt mere udtalt i de akustiske kerner og -baner i cerebrum Det anses derfor mest sandsynligt, at de akustiske udfaldssymptomer er centralt såvel som perifert betingede hvadenten det gælder lav eller højfrekvensområdet.

De vestibulære udfaldssymptomer synes derimod at være udelukkende centralt betingede, idet der er et åbenbart misforhold mellem den svært nedsatte kaloriske reaktion på begge ører og de tilsyneladende normalt udseende dele af labyrintherne, inclusive 1 neuron *samtidigt med at man ser overordentlig svære forandringer* indenfor de vestibulære kerner og baner i hjernestammen

Kapitel VI omfatter en beskrivelse af materialet og af de metoder der er benyttet ved udtagningen de eksperimentelle karinjektioner samt dissektionen af 43 tindingeben fra mennesker i alle aldersgrupper Ud fra dette materiale har man forsøgt at finde en forklaring på visse af de patologisk-anatomiske forandringer der omtales i afsnit 1

I *Kapitel VII* omtales dels karforbindelserne mellem den membranøse labyrinth og dens otiske kapsel dels fyldningsmønstret i visse områder af cochleas kar

I alle tindingeben i *hvilke kontraststofferne fylder modioluskar svarende til basale cochleavinding (ialt 31)* trænger kontrasten direkte ud i den otiske kapsels enchondrale lag via den løst strukturerede knoglehylde, der adskiller basale og mellemste vinding Såvel arterielle som venøse anastomoser *mellem ekstra og intralabyrinthære* kar kan påvises. I alle cochleavindinger findes kar der gennem det endosteale lag, forbinder det intracochleære karnet og den otiske kapsels kar Disse karforbindelser etableres dels via canaliculi af kapillærkaliber mellem selve *det endosteale lags* knoglefibriller dels via arterioler der udgår fra arteriolae rectae i scala vestibuli Anastomoser af alle de nævnte typer kan demonstreres i tin

dingeben fra patienter i alle aldersgrupper de er set hos et 5 dage gammelt barn såvel som hos patienter over 90 år De kan tillige fyldes ved injectioner i såvel intra- som ekstracranielle kar der forsyner tindingebenet. *De intralabyrinthære arterier er således ikke endearterier*

Intracochleært synes karforsyningen til basale vindings strukturer at være rige lige, specielt i området omkring ganglion spirale cochleae. Endvidere ses god fyldning ud i membrana basilaris, uanset graden af de degenerative forandringer i det Cortiske organ, der kan iagttages ved hjælp af osmiumsyrefarvningerne. Der ses endvidere forbindelseskar mellem stria vascularis og membrana basilaris via membrana Reissneri.

Kapitel VIII Karinjektionsmønstret i den otiske kapsel beskrives tindingebensmaterialet er det samme som det, der omtales i kapitel VII Man ser i tindingeben fra patienter i alle aldersgrupper at specielt det enchondrale lag er velforsynet med kar Disse kar kan injiceres fra ekstra- såvel som intrakranielle arterier Ved injektion fra begge karområder i samme præparat, kan der endvidere demonstreres end-to-end anastomoser af arteriolekalliber mellem disse Ved sådan dobbeltinjektion findes endvidere arterio-venøse anastomoser af lignende kaliber

De bedst fyldte knogleregioner er dels dem, der ligger medialt for fossa subarcuata, med tilløb af intrakranielle kar specielt fra a. subarcuata, dels det område, der anteriort-posteriort skiller vestibulum fra cochlea (indefattende knoglebyiden mellem basale og mellemste vinding) samt, medialt-lateralt, canalis auditorius internus fra mellemørets promontorium.

Gennem dette karnet kan man følge kar der fra intracochleære strukturer ubrudt forløber gennem 2 eller 3 lag i den otiske kapsel til, blandt andet, mellemørets strukturer og carotiskar som f.eks. a. carotis interna i dens forløb gennem canalis caroticus.

Kapitel IX Karforsyningen i nervus acusticus diskuteres. Det gælder for alle aldersgrupper at karnettet er rigeligere og mere regelmæssigt i nervernes Schwannske del end i deres gliøse afsnit. Overgangen mellem de to injektionsmønstre i canalis auditorius synes skarp.

Kapitel X indeholder en sammenfattende konklusion og diskussion af de i afsnit 1 og 2 omtalte fund

Afsnit 1 Ved hjælp af de lysmikroskopiske metoder der har været til rådighed har man skønnet, at de degenerative forandringer i labyrinthens strukturer er langt mindre udtalte end de forandringer der er tilstede i hjernens hørebaner og centre hos 14 patienter med perceptionshøretab specielt høretab af presbyacusis-type Det perifere høreorgan synes endog at være normalt hos to patienter med presbyacusis Den Schwannske del af *nervi acustici* er tilsyneladende velbevaret til trods for svære arteriosclerotiske forandringer i de kar der passerer gennem canalis auditorius internus ekstraneuralt, hvorimod nervernes gliøse del ses at være degenereret i samme grad som den hvide substans i de cerebrale hemisfærer I cochlea er udfald og degeneration af celler i ganglion spirale cochleas basale vinding det

eneste pathologiske fund, der ikke synes at kunne tilskrives postmortelle forandringer omend udfald og degeneration ikke er proportionale med de observerede højttonehøretab

Man må således konkludere, at årsagen, eller årsagerne, til de klinisk fundne høretab skal søges i såvel centrale som perifere afsnit af det auditive system hos to af de her omtalte patienter med presbycusis syntes høretabet dog udelukkende cerebralt betinget.

Afsnit 2 Resultaterne af de eksperimentelle injektioner i kar i 43 tindingeben fra patienter i alle aldersgrupper beskrives med det formål at forklare de perifere læsioner man har observeret hos de i afsnit 1 omtalte patienter Det fremgår at cochleas arterier ikke er endearterier men at de forbinder sig med karrene i den otiske kapsel, specielt rigeligt svarende til basale cochleavinding, og videre ud til mellemørets strukturer samt direkte til carotisgrene Fyldning af cochleae kan således også ske ved injektion af carotisgrene Disse anastomoser kan demonstreres i tindingeben fra patienter i alle aldersgrupper· i dette materiale blev også den otiske kapsel velfyldt med kontrast, selv i præparater fra gamle patienter med svær universel *arteriosclerose Den således demonstrerede blodforsyning via den otiske* kapsels kar kan derfor muligvis forklare at man i det kliniske materiale omfattende gamle patienter (afsnit 1) finder velbevarede strukturer i mellemste og apicale cochleavindinger Karinjektionerne forklarer derimod ikke hvorfor specielt basale *cochleavindings strukturer er degenererede idet karanastomoserne*, via den otiske kapsel, til denne del af cochlea findes at være specielt rigelige De degenerative forandringer man, ved osmiumsyrefarvning af det Cortiske organ, har kunnet finde i basale cochleavinding i tindingeben fra senile patienter med universel arteriosclerose, har heller ikke kunnet forklares ved kontrastofinjektionerne idet kontrasten i disse tilfælde har udfyldt endog vas membranae basilaris i tindingeben fra disse

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From the Section of Otolaryngology Department of Surgery
Yale University School of Medicine, USA

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Introduction

Because of its relation to the cricoid cartilage and to the pharyngo-esophageal junction, the cricopharyngeus muscle (CP) has both a laryngeal and pharyngeal function. It acts as an accessory tensor of the vocal cord in singing (Sonninen, 1968 Zenker W and Zenker A. 1960) and in the reflex protective closure of the larynx (Murakami and Kirchner 1971 *a*).

Cricopharyngeal spasm may be caused by an intraluminal foreign body resulting in its being trapped at the esophageal entrance. Some cases of dysphagia have been attributed to cricopharyngeal spasm and "autonomic imbalance Rogers (1935) reported a case of dysphagia cured by bilateral excision of the superior cervical sympathetic ganglion. Some authors have since then proposed that a sympathetic nerve supply to the muscle causes contraction, and the parasympathetic causes relaxation (Sjoberg, 1939 Bolerkamp, 1957 *Kirchner 1958*).

Other reports, however reflect doubt on the nerve supply to the CP and even on its type of muscle. In this regard, Lund and Ardran (1964) observed no responses in the CP to stimulation of the vago sympathetic. Levitt et al (1964) concluded, on the basis of EMG studies, that there is no sympathetic motor nerve supply to the CP On the other hand, Kramer et al (1957) reported two cases of CP paresis cured by prostigmine.

Despite these disagreements, and even though its functional components have not been clearly identified, the motor nerve supply to the CP at least in the dog and cat, is generally agreed to be the pharyngo-esophageal or descending pharyngeal nerve (Hwang, 1948).

The precise mechanism of the muscle s sphincteric action has never been clearly de scribed, although it has been studied for over 150 years (Bosma, 1957). It is generally agreed that a zone of increased pressure exists within the CP area at rest, and that this pressure drops only during the act of swallowing (Fyke and Code, 1955). Levitt et al. (1964) concluded that the phasic inspiratory activity which they observed in the CP is controlled by the respiratory center Murakami and Kirchner (1972 *b*) observed motor units in the CP which discharge during inspiration, others which discharge during expiration, and suggested that this combination may explain the muscle s tonic contraction.

In the present study Part I is an electrophysiological investigation of the nerve supply and reflex responses of the CP muscle. Part II is a study of the muscle s responses to various cholinergic and adrenergic agents, as a means of demonstrating its involuntary characteristics and its relation to the autonomic nervous system.

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PART I

Electrophysiological Properties

Yasushi Murakami M.D Hiroyuki Fukuda, M D and
John A Kirchner M D

METHODS

Fifty-one adult cats were used in these experiments Light anesthesia was maintained by intraperitoneal injection of 25–30 mg/kg of Nembutal Maintenance doses were given through an intravenous cannula in the basilic vein This cannula was also used for administration of the various drugs under study The CP muscle was exposed by a midline skin incision Low tracheotomy and cannulation were performed.

The sternohyoid and sternothyroid muscles were removed for exposure of the laryngeal nerves Both superior laryngeal nerves (SLN) were cut in order to eliminate artefacts from reflex contraction of the cricothyroid muscles, and to prepare the internal branch of the nerve for electrical stimulation (2 msec. 0.5–1 0 V)

The recurrent laryngeal nerve (RLN) was cut bilaterally to eliminate artefacts due to laryngeal movements, current spread from the internal laryngeal muscles and intraluminal pressure changes resulting from arytenoid movements A pair of recording electrodes supported the central cut end of the left RLN A spiral copper wire recording electrode was placed on the surface of the CP muscle and another on the thyropharyngeus muscle as a control

EMG potentials were displayed on a multichannel oscilloscope (Tektronix 564B) after amplification, monitored by another oscilloscope (Tektronix 561A) through a preamplifier (Tektronix 122). Two audiosystems, then recorded by Grass camera.

Contraction of the CP muscle during electrical stimulation of various nerve fibers was visually observed through a surgical microscope. The degree of contraction was reflected by an intraluminal pressure change which was measured by a closed circuit water filled pressure transducer (Statham P23PC) (Murakami and Kirchner 1971 a)

To maintain the precise location of the pressure transducer within the CP segment, the esophagus was opened the transducer introduced upward into the CP segment and tied into position. Further the left vagus was cut low in the neck to eliminate possible artefacts resulting from descent of the esophagus and the cricoid. The nodose ganglion of the vagus and anterior sympathetic cervical ganglion (ASCG) were prepared for individual stimulation.

Nerve recordings were made from the cricopharyngeal nerve (see Fig. 1) and from two major branches which form the pharyngeal plexus. Potentials in the nerve were amplified by DAM 5 then displayed on these oscilloscopes. Immobilization of the animals by injection of Flaxedil was used to eliminate artefacts from cough, swallowing etc.

RESULTS

1 *Neuroanatomy of the cricopharyngeus muscle*

Contraction of the CP muscle was consistently observed with stimulation of the cricopharyngeal nerve (CPN) but never by the RLN Large evoked potentials during RLN stimula-

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RESULTS

1. Neuroanatomy of the cricopharyngeus muscle

Contraction of the CP muscle was consistently observed with stimulation of the cricopharyngeal nerve (CPN) but never by the RLN. Large evoked potentials during RLN stimula-

charges in the nerve was almost the same as in the RLN (20–25 msec), while that in the muscle was much longer (45–50 msec) indicating continuing activation of the CP muscle by afferents in the CPN itself (Fig. 2)

This concept is supported by the next experiment. Reflex responses of short latency were frequently recorded from the central cut end of the longer branch by stimulation of that of the shorter branch. This can be termed a pharyngo-pharyngeal reflex and is probably the cause of the cricopharyngeal spasm in the presence of an intraluminal foreign body (Fig 3 A).

Another pathway of the pharyngo-pharyngeal reflex was detected in the glossopharyngeal nerve stimulation of which induced reflex responses in the CPN with a moderate latency The threshold for this reflex was much higher than for the SLN or the CPN itself (Fig. 3 B)

In a previous study of reflex activation of the laryngeal muscles, laryngospasm was shown to be due to after-discharges occurring mostly in the thyroarytenoid muscle, following cessation of stimulation (Murakami and Kirchner 1972). Similarly with stimulation of the internal branch of the SLN the CP muscle or its nerve displayed the same type of after-discharges. These discharges were of larger voltage than spontaneous tonic discharges, and are most likely the source of cricopharyngeal spasm. For want of a better term, these discharges are referred to as spasmic after-discharges"

With repetitive single shocks (1 per sec) they gradually appeared in increasing number and continued for ten to thirty seconds after cessation of stimulation (Fig. 4). With high frequency stimulation of the internal branch of the SLN discharges in the CP muscle or its nerve appeared at once and continued for some seconds afterward (Fig. 5).

Intraluminal pressure increased with every reflex shock stimulus. The increase was less than that seen in direct stimulation of the CPN The results indicate that the CPN is

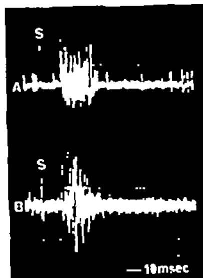


Fig 3 Pharyngo-pharyngeal reflexes (A) Responses were evoked in the longer branch of the pharyngeal plexus by single low-voltage stimulation of the shorter branch This may be responsible for reflex contraction or spasm of the cricopharyngeus in the presence of intraluminal foreign body (B) Strong (3 0 V 0 1 msec) stimulation applied to the glossopharyngeal nerve induced reflex responses in the cricopharyngeal nerve Note shorter latencies than in the laryngo-pharyngeal reflex in Fig.

composed of several kinds of nerve fibers and that only some of them respond to reflex stimulation. Many other motor fibers including vagal or sympathetic tonic fibers are reflexly inhibited or simply show no reflex response (Fig 6).

After the shorter branch was cut, the CPN was prepared for both stimulating and recording electrodes. Stimulation at various frequencies produced no reflex discharges. This indicates that all of the afferent fibers from the CP muscle reach the vagus trunk from the shorter branch. Afferents in the longer branch then, most likely originate in the thyropharyngeal or hyopharyngeal areas (Fig. 1)

3 *Reflex responses of background activity in the cricopharyngeus muscle*

The CP muscle exhibits a tonic background activity at least under light anesthesia, regardless of the respiratory cycle (Murakami and

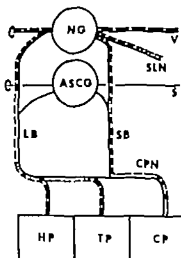


Fig 1 Diagram indicating innervation of the cricopharyngeus muscle Motor neurons, vagal and sympathetic, come through both shorter and longer branches of the pharyngeal plexus, while the afferents pass only through the shorter one Solid and dotted lines indicate efferents and afferents respectively *CP* Cricopharyngeus muscle *TP* thyropharyngeus muscle *HP* hyopharyngeus muscle (middle constrictor) *CPN* cricopharyngeal nerve *SB* shorter branch *LB* longer branch (pharyngo-esophageal nerve), *ASCG* anterior sympathetic cervical ganglion *NG* nodose ganglion *V* vagus nerve *SLN* superior laryngeal nerve

tion before sectioning were clearly shown to be due to current spread from the laryngeal muscles, especially from the posterior cricoarytenoid. Since the CPN was the only nerve that produced consistent responses in the CP muscle an analysis of its functional components was made

Two major branches of the pharyngeal plexus diverge from the vagus nerve the longer branch (the pharyngo-esophageal nerve) leaving the vagus at the cranial end of the nodose ganglion and the shorter branch leaving at the same level as the SLN The longer branch ramifies into small nerves which innervate the hyopharyngeus (middle constrictor) and the thyropharyngeus muscles to form the CPN (Fig 1) The latter nerve shows many turns as it enters the muscle

The central cut end of both the longer and shorter branches showed spontaneous tonic activity regardless of the respiratory cycle This tonicity continued even after sectioning the vagus nerve at its entrance into the skull and, in some other cats, after removal of the ASCG The results indicate that both the longer and shorter branches contain efferent nerve fibers of both vagal and sympathetic origin and that some of these efferents possess a spontaneous tonic activity at least in light stages of anesthesia

From observations in previous studies the CPN contains afferent fibers which evoke reflex responses in the RLN The RLN responded well to stimulation of the shorter branch in all cases, but only occasionally to stimulation of the longer branch. Most of the afferent fibers therefore are carried by the shorter branch.

2. *Reflex discharges and spasm in the cricopharyngeus muscle*

The CP muscle responded reflexly to stimulation of the internal branch of the SLN Latency was much longer than that in the RLN indicating a greater number of synapses in this reflex pathway The duration of dis-

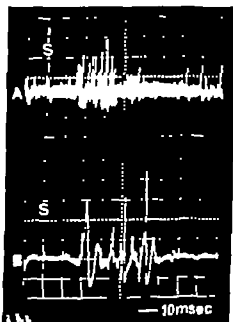


Fig 2 Reflex responses evoked in the cricopharyngeal nerve (A) and in the EMG of the cricopharyngeal muscle (B) by single shock stimulation of the internal branch of the superior laryngeal nerve Note long duration of activity in B, indicating continuing activation of the cricopharyngeal muscle by afferent impulses carried by the cricopharyngeal nerve itself

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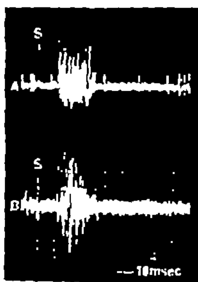


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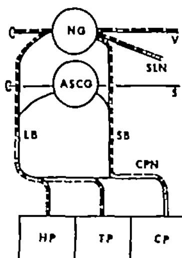


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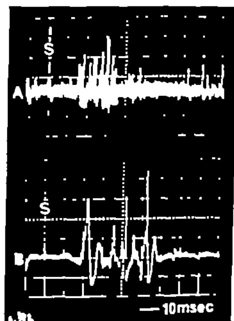


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Kirchner 1972 b) Many of these discharges originate in the vagus nerve and a few others in the sympathetic, because many of them disappeared after the vagus nerve was sectioned above the nodose ganglion.

With every stimulation of the internal branch of the SLN tonic activity originating in the vagus nerve was briefly inhibited, probably indicating reflex inhibition of the respiratory center It is probable that this tonic fiber is anatomically different from those which are reflexly activated. This could not be verified because of the difficulty in preparing single nerve fibers of the tonic group.

After the nodose ganglion was removed or damaged, tonic activity was still observed in the CPN although it was very sporadic and low in voltage. This activity is probably mediated through the ASCG With the nodose ganglion removed, repetitive stimuli applied to the central stump of the vagus produced no detectable reflex discharges in the CPN However tonic activity in the CPN gradually increased under

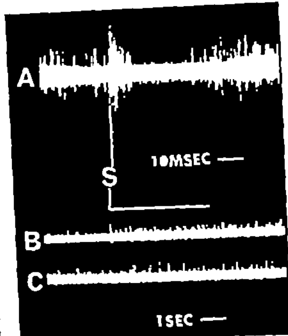


Fig 7 (A) High-speed recording from the cricopharyngeal nerve after damaging the anterior sympathetic cervical ganglion, showing reflex discharges and inhibition of tonic background activity with single shock stimulation of the internal branch of the superior laryngeal nerve. (B and C) (continuous recording) show that the tonic activity in the cricopharyngeal nerve after removal of the nodose ganglion originates in the anterior sympathetic cervical ganglion. It gradually increases in frequency with repetitive stimulation of the central stump of the vagus.

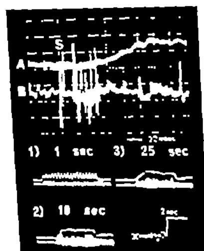


Fig 6 Increase in intraluminal pressure (upper traces) reflecting reflex contraction of the cricopharyngeal muscle (EMG lower traces) with stimulation of the internal branch of the superior laryngeal nerve at different frequencies, 1/sec, 10 sec and 25/sec. Note that the slow pressure increase in the high-speed recording at top and that the degree of increase at the most effective stimulus frequency (25 sec) is not much higher than in single shock or direct stimulation of the motor nerve.

this stimulation. These results indicate that. 1) the nerve fibers that discharge reflexly originate in the vagus, and 2) tonic activity in the sympathetic supply to the muscle increases gradually during stimulation of vagal afferents (Fig. 7).

4. *Differences between stimulation of the vagus nerve and of the sympathetic ganglion*

In some animals the vagus nerve was prepared for stimulation up to its entrance into the skull, preserving the nodose ganglion and two major branches which form the pharyngeal plexus and innervate the CP muscle. Direct stimulation at 1.0 to 3 0 volts was delivered to the vagus nerve just above the level of the nodose ganglion. Both directly evoked and

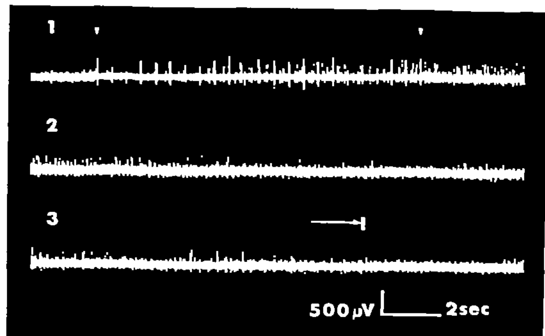


Fig 4 Reflex and after-discharges were evoked in a continuous EMG recording of the cricopharyngeal muscle activity during repetitive single shock stimulation of the internal branch of the superior laryngeal nerve (?/sec, 0.5 V 0.1 msec) between triangular marks in line (1). Small white dots indicate stimuli. Note that spontaneous activity gradually increased and that larger after-discharges lasted for about 30 seconds after cessation of stimulation. Arrow indicates cessation of after-discharges. Duration of after-discharges varied with depth of anesthesia.

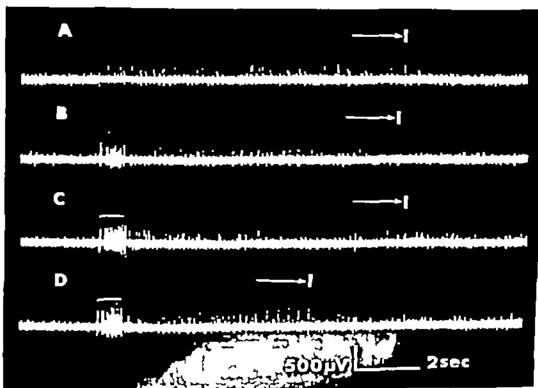


Fig 5 Duration of after-discharges recorded in EMG of the cricopharyngeal muscle by stimulation of the internal branch of the superior laryngeal nerve at different frequencies, 10/sec in A 20/sec in B 30/sec in C and 70 sec in D. Note shorter duration in D indicating that high frequency stimulation not particularly effective. At lower stimulation frequencies, duration of after-discharges is about the same.

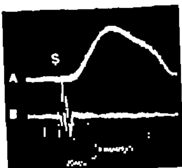


Fig 12 Evoked potentials in the cricopharyngeal muscle and intraluminal pressure increase induced by single direct stimulation of both shorter and longer branches of the pharyngeal plexus Note multiphasic potentials and slow pressure increase.

and intraluminal pressure increased. The evoked EMG potential showed a complicated and prolonged wave form, reflecting different conduction velocities among fibers of the various sizes in the CPN (Fig. 12).

The greatest increase in intraluminal pressure with single shock stimulation was 36 mm H_2O at 65–75 msec after activation, reflecting the contraction time of this muscle. Forty-five to fifty msec were required for the pressure to drop to half The half-relaxation time of this muscle is apparently much longer than that of the laryngeal muscles (Murakami and Kirchner 1972 *a*; Mårtensson and Skoglund, 1964 Hast, 1967 *a*, 1967 *b*).

The highest pressure increase (110 mm H_2O) was observed with stimulation at a rather low frequency (20/sec), which is equal to the fusion frequency of the muscle. Tetanus-twitch ratio then is about 3 (Fig. 13)

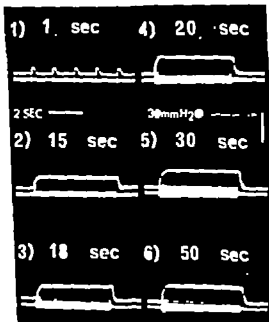


Fig 13 Intraluminal pressure increase (upper traces) reflecting the degree of cricopharyngeal muscle contraction (low traces) with single or repetitive stimulation of the motor nerve. The highest pressure occurred at relatively low frequency of stimulation (20 sec)

DISCUSSION

The CP muscle is classified as a striated muscle. In contrast to the usual somatic muscle, however its activity is not voluntarily regulated, being inhibited or activated in the course of deglutition as part of a group of muscles systematically controlled by the central nervous system. Moreover the CP exhibits characteristics of slow muscle contracting and relaxing more slowly than the laryngeal muscles (Mårtensson and Skoglund, 1964 Hast, 1967 *a* 1967 *b*) Tetanus-twitch ratio is only 3 indicating a lower innervation-ratio, an arrangement which might be useful for the tonic contraction of a sphincter muscle.

The mechanism of CP spasm in the presence of foreign body is explainable on the basis of these studies. Stimulation of afferent receptors in the pyriform sinus, post-cricoid area or uppermost cervical esophagus evoked reflex contraction and spasm in the CP muscle. Direct stimulation of the mucosa by the tip of the manometer however did not provoke spasm after the SLN had been sectioned. If the SLN is left intact, severe coughing during stimulation by the manometer makes experiments impossible In deeper stages of anesthesia there was no response whatever

In sharp contrast to the CP muscle the thyropharyngeus showed no reflex activation whatever during these experiments.

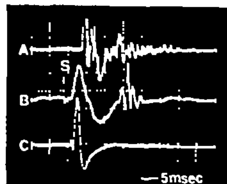


Fig 8 Direct stimulation of the vagus nerve just above the nodose ganglion induced two kinds of discharges, evoked and reflex, in the recurrent laryngeal nerve (A) and in the EMG of the cricopharyngeal muscle (B) By contrast, only an evoked potential was induced in the thyropharyngeal muscle (C)

reflex discharges appeared in the RLN and in the CP muscle In sharp contrast to the CP the thyropharyngeus muscle showed only an evoked potential but never the reflex discharge (Fig 8) Intraluminal pressure increased sharply with each stimulus even after the ASCG was eliminated (Fig 9)

Direct stimulation of the ASCG induced evoked potentials in the CP muscle but never in the thyropharyngeus muscle. Latency was about 7 msec, much longer than with vagus stimulation These results indicate that sympathetic fibers supply only the CP portion of the inferior constrictor and that the conduction velocity of the sympathetic nerve fibers is much slower than that of motor fibers in

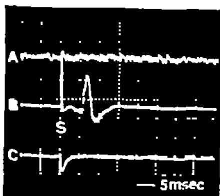


Fig 10 Direct stimulation of the anterior sympathetic cervical ganglion induced evoked potential in the cricopharyngeal muscle (B) but not in the thyropharyngeus (C) or in the recurrent laryngeal nerve (A). The latency in (B) indicates very small diameter fibers (sympathetic) with slow conduction velocity By comparison, Fig. 8 (B) shows a very short latency with stimulation of the vagus indicating large diameter fibers.

the vagus (Fig 10) Contraction of the CP muscle and increase in intraluminal pressure were observed during ASCG stimulation (Fig 11)

5 Contraction properties of the Cricopharyngeus muscle

After small branches which innervate the thyropharyngeus and the hyopharyngeus muscles had been sectioned both the longer and the shorter branches of the pharyngeal plexus were placed on the stimulation electrodes. With every stimulus, the CP muscle contracted

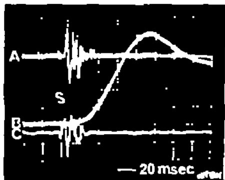


Fig 9 Direct stimulation of the vagus nerve just above the nodose ganglion induced intraluminal pressure increase (B) reflected by both evoked and reflex activity in the cricopharyngeus (C). This was true even after removal of the anterior sympathetic cervical ganglion Similar discharges were also evoked in the recurrent laryngeal nerve (A)



Fig 11 Direct stimulation of the anterior sympathetic ganglion induced an evoked potential in the cricopharyngeal muscle (C) but not in the recurrent laryngeal nerve (A) The lower increase in intraluminal pressure recorded at the same gain as in Fig. 9 (B), indicates a lower number of sympathetic fibers than vagal

PART II

Neuropharmacological Properties

Hiroyuki Fukuda, M.D and John A. Kirchner M.D

In Part I of the present study two components, vagal and sympathetic, were identified in the innervation of the cricopharyngeus muscle (CP) For a clearer understanding of the involuntary characteristics of the muscle and its relation to the autonomic nervous system the muscle s responses to various adrenergic and cholinergic agents were studied and are here reported as Part II.

Adrenergic effects were studied with the following agents:

1) methoxamine (Vasoxyl[R]) an alpha stimulator

2) phentolamine (Regitine[R]) an alpha blocker

3) isoproterenol (Isuprel[R]) a beta stimulator

4) propanolol (Inderal[R]) a beta blocker

5) imipramine (Tofranil[R]) an anti-depressant which decreases re-uptake of norepinephrine at adrenergic nerve endings.

Cholinergic effects were studied with the following

1) neostigmine (Prostigmine[R]), an anti-cholinesterase,

2) atropine, a muscarine blocker

3) gallamine (Flaxedil[R]) a nicotine blocker

The dose level for each drug was arrived at by using, first, the recommended dose per unit weight, then adding more drug until an effect was obtained This usually proved to be two to three times the recommended dose.

Forty-one cats were used in Part II five or more for each drug Recording and stimulating techniques are detailed in Part I of this report

RESULTS

I Adrenergic agents

Methoxamine HCL, a predominantly alpha stimulator was injected intravenously in 10–20 mg amounts. About 30 seconds after administration spontaneous tonic activity appeared in the CP muscle and continued more than 30 minutes if a blocking agent was not given If an alpha-adrenergic blocking agent was given (phentolamine, 5 mg) this activity became weak or stopped completely within 60 seconds As a control, the thyropharyngeus showed no tonic activity after administration of methoxamine (Fig. 14)

Propanolol HCL, a beta-blocking agent, had no effect on the activity produced by methoxamine. Similarly a beta-stimulator isoproterenol HCL, produced no discernible activity in the CP

Stimulation of the internal branch of the superior laryngeal nerve (SLN) at 20 cps or more produced both reflex and after-discharges in the CP Duration of the after-discharges was longer under light anesthesia than under deep, and longer after methoxamine (Fig. 15).

Imipramine (less than 1 mg/kg) inhibited the activity of the CP which had been induced by methoxamine. This inhibition was complete within 20 seconds after injection of imipramine. Methoxamine-induced activity usually continues for about 30 minutes (Fig. 16).

Similarly tonic activity in the CP was observed with neostigmine, an anti-cholinesterase agent. The activity was not so strong, however as that produced by methoxamine (Fig. 17)

Neuroanatomically the CP is characteristically supplied by sympathetic nerve fibers which discharge tonically giving the muscle a constant tonus as an esophageal sphincter Sympathicotonic influences, then might cause hypertonicity of the CP muscle

Cricopharyngeal spasm in the presence of a pharyngo-esophageal foreign body is probably produced by a combination of spasmic motor discharges of vagal origin and hyper activity of the sympathetic supply

SUMMARY AND CONCLUSIONS

1 The cricopharyngeus muscle is innervated by both vagal and sympathetic components.
2. The cricopharyngeus muscle exhibits a tonic activity which is independent of the respiratory cycle It originates in both the vagal and the sympathetic nerve supplies.
3 The cricopharyngeus muscle contracts reflexly in response to stimulation of laryngopharyngeal afferents (through different pathways from each other).
4 Reflex activation of the cricopharyngeus is followed by after-discharges which may be responsible for spasm This activation is mediated by motor neurons in the vagus nerve
5 Tonic activity of sympathetic origin increases during stimulation of laryngo-pharyngeal afferents.

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5 Tonic activity of sympathetic origin increases during stimulation of laryngo-pharyngeal afferents.

2. *The effect of adrenergic drugs on reflex activity*

With every single-shock stimulation of the internal branch of the SLN a reflex discharge was observed in the CP and a contraction of the muscle which was proportional to the degree of discharge.

In Fig. 18 the EMG of the CP and of the tongue musculature are displayed during stimulation of the internal branch of the SLN at 0.5 V. The CP shows a very small reflex discharge under normal conditions, but a strong and prolonged response after administration of methoxamine (Fig. 19). By contrast, the reflex response in the tongue muscle, of skeletal type, was not influenced by methoxamine (Figs. 18, 19).

Similarly an alpha-blocking agent, phentolamine, reduced the amplitude and duration of reflex response in the CP but did not affect that in the tongue (Fig. 19).

3. *Effect of cholinergic drugs on reflex activity*

Neostigmine (0.3–0.5 mg) prolonged and accentuated the reflex response in the CP. This effect was inhibited by atropine, a cholinergic blocking agent, but not so dramatically as phentolamine inhibits methoxamine-induced

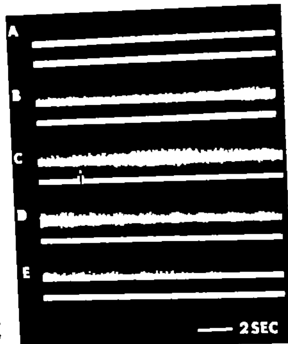


Fig. 16. Inhibition by imipramine of methoxamine-induced activity. Upper traces: EMG of cricopharyngeus. Lower traces: EMG of thyropharyngeus. (A) Before administration of methoxamine. (B) After administration of methoxamine, the activity of the cricopharyngeus muscle gradually increases. (C) After injection of imipramine (arrow) cricopharyngeus activity increases initially for about 5 seconds. (D) The cricopharyngeus activity gradually decreases. (E) Cricopharyngeus activity stops, in this case within 20 seconds after imipramine. A and B, C–E are continuous recordings.

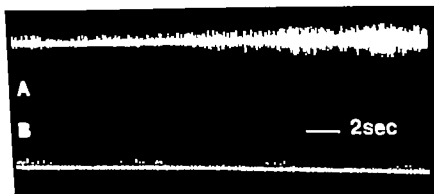


Fig. 17. Effect of adrenergic and cholinergic stimulation on cricopharyngeal tonicity. (A) Methoxamine effect. (B) Neostigmine effect. Each agent was injected about 70 seconds before the beginning of each tracing. The cricopharyngeus was completely silent on EMG before administration of the drug in each case. Both tracings made in the same cat.

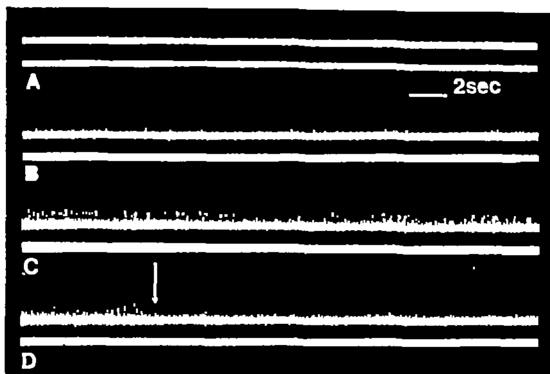


Fig 14 Effect of alpha-adrenergic agents on tonic activity in the cricopharyngeus muscle Upper traces cricopharyngeus muscle. Lower traces thyropharyngeus muscle. (A) Before administration of methoxamine, the cricopharyngeus muscle is completely silent at this level of anesthesia. (B) 30 seconds after administration of methoxamine, an alpha stimulator (C) 70 seconds after administration of methoxamine. (D) Gradual inhibition of tonic activity by phentolamine an alpha blocker Note absence of effect on the thyropharyngeus portion of the inferior constrictor muscle (lower traces)

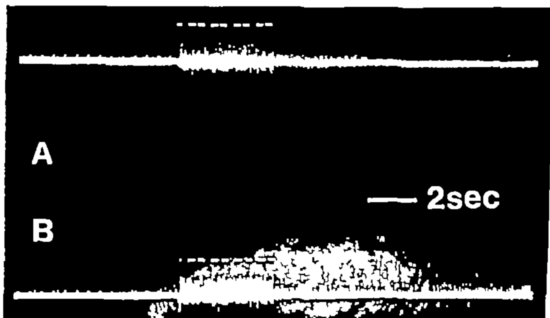


Fig 15 Reflex and after discharges in EMG recordings of the cricopharyngeus muscle by repetitive stimulation of the internal branch of the superior laryngeal nerve (30 sec, 0 7 V) (A) Before administration of methoxamine (B) After administration of methoxamine Note increased duration of after discharges

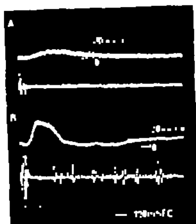


Fig 21 Increase in intraluminal pressure at cricopharyngeus with adrenergic agents (A) Before methoxamine administration peak pressure (top) is less than 25 mm H₂O. (B) After methoxamine administration peak pressure is higher and occurs earlier. EMG of cricopharyngeus lower traces. Same animal in A and B

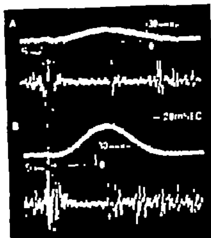


Fig 23 Intraluminal pressure produced by single shock stimulation of the internal branch of the superior laryngeal nerve in control cat (A) Stimulation 1 volt. (B) Stimulation 5 volts. Magnitude of reflex pressure increase is directly proportional to intensity of stimulus, but peak pressure occurs at the same time interval regardless of stimulus strength. This is not true after methoxamine, when the peak pressure occurs much earlier after stimulation (compare Fig 21)

sures occurred more quickly and attained levels of 33 mm H_2O and higher (Fig. 21)

With neostigmine, peak pressure was nearly the same as for the control, both in magnitude and in time (Fig. 22)

Magnitude of reflex pressure was directly proportional to the intensity of stimulus delivered to the SLN (Fig. 23). By contrast, the time at which peak pressure occurred after single shock stimulation was always the same, regardless of stimulus strength

In Fig. 24 superimposed pressure curves compare the effects of methoxamine and neostigmine with controls. Methoxamine produces the quickest pressure rises both with single and repeated stimulation.

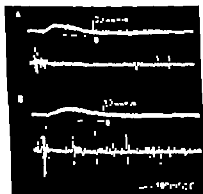


Fig 22 Increase in intraluminal pressure at cricopharyngeus with cholinergic agents. Single shock stimulation applied to internal branch of the superior laryngeal nerve in the same cat (A) Before neostigmine (B) After neostigmine. Resting pressure is higher and peak pressure slightly higher. The difference is not so great as with adrenergic agents (see Fig 21)

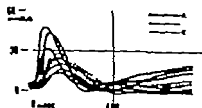


Fig 24 Schema of the curves indicating the onset and degree of pressure increase traced from actual photographs (A) After administration of methoxamine. (B) Normal control. (C) After administration of neostigmine. Peak pressure occurs earliest after methoxamine. Peak pressure is also higher after neostigmine than in the control, but time of occurrence is nearly the same.

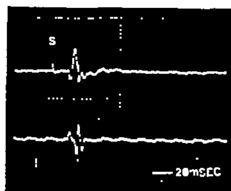


Fig 18 Reflex induced in the cricopharyngeus muscle and in the tongue muscle by single shock stimulation of the internal branch of the superior laryngeal nerve (control for Figs. 19 and 20) Upper trace evoked EMG in cricopharyngeus muscle. Lower trace evoked EMG in tongue muscle.

activity The effect on the reflex response in the tongue muscle was very small (Fig 20)

4 *Effect of neuromuscular blocking agents on reflex response*

Gallamine which competes with acetylcholine at the end-plate receptor in skeletal muscle,

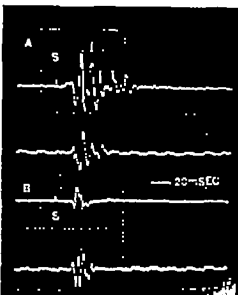


Fig 19 Effect of alpha-adrenergic agents on reflex excitability of cricopharyngeus and of tongue muscle Single shock stimulation applied to internal branch of the superior laryngeal nerve in the same cat. (A) After methoxamine administration reflex responses prolonged in cricopharyngeus (upper trace) as compared with tongue (lower trace) and with control in Fig 18 (B) After phentolamine (alpha blocker) had been added reflex response in cricopharyngeus (upper trace) returns to normal duration. No change in response of tongue musculature

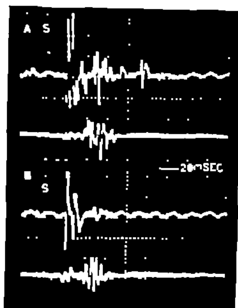


Fig 20 Effect of cholinergic agents on reflex excitability of cricopharyngeus and of tongue muscle. Single shock stimulation applied to internal branch of the superior laryngeal nerve in the sam cat. (A) After neostigmine administration, reflex response is prolonged in cricopharyngeus (upper trace) as compared with tongue and with control in Fig. 18 (B) After atropine administration (less than 1 mgm) reflex response in cricopharyngeus (upper trace) returns to normal duration. No change in response of skeletal muscle of tongue.

was used as a neuromuscular blocking agent.

After reflex discharges were recorded in the CP and the tongue muscles to single shock stimulation of the SLN gallamine (0 2 mg or less) was injected intravenously In three cats of the five reflex responses to SLN stimulation ceased simultaneously in both the CP and the tongue muscles. In two other cats, reflex discharges were obtained for a slightly longer time in the CP than in the tongue muscles (25 vs. 20 sec) The difference is probably of no significance.

5 *Intraluminal pressure changes induced by various agents*

Consistent intraluminal pressure increases at the CP occurred with each single shock stimulation of the internal branch of the SLN (1 0 V in all cases.)

Without drugs, peak pressures were less than 25 mm H_2O After methoxamine peak pres-

constrictor muscle and the tongue musculature were not influenced by any of these drugs,

(4) The cholinergic agent affected chiefly the CP muscle

Moreover adrenergic fibers play an excitatory role, whereas cholinergic fibers provide background tonicity since

(1) Intraluminal pressure increase after electrical stimulation of the internal branch of the SLN was more rapid after injection of the adrenergic agent than of the cholinergic

(2) Spontaneous tonic activity induced by the adrenergic agent was stronger than that produced by the cholinergic.

If then abnormal spasm of the CP is due to autonomic imbalance this imbalance may be within the adrenergic or cholinergic group itself rather than between the two and probably the *former*

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DISCUSSION

The site of action of acetylcholine one of the neural mediators, is at the postganglionic para *sympathetic effector organ (muscarinic ac tion)* synaptic transmission in all autonomic ganglia and transmission from motor fiber to skeletal muscle (nicotinic action) It is generally believed that the effect of acetylcholine on smooth muscle is more prominent than that on skeletal muscle. Acetylcholine is de stroyed promptly by cholinesterase, so that the effect of acetylcholine can be accentuated by using cholinesterase inhibitors, as for ex ample neostigmine.

A cholinesterase inhibitor has two actions one muscarinic, for excitation of involuntary *muscle the other nicotinic, for excitation of* skeletal muscle. The former is inhibited by atropine and the latter by curare The muscarinic action of neostigmine is probably produced by cholinesterase inhibition whereas its nicotinic action at least at the neuromuscular site is in part due to a direct effect on the muscle *The latter action requires relatively* large amounts of neostigmine.

After injection of less than 0.5 mg of neostigmine reflex contraction of the CP mus *cle to electrical stimulation of the internal branch of the SLN was stronger and con* tinued for a longer time than normally By contrast with skeletal muscle, there was al most no change in the responses of the tongue musculature. Moreover if atropine was administered immediately after the onset of the neostigmine effect reflex responses soon diminished to normal levels. It seems, therefore that the CP reacts physiologically like an in voluntary muscle.

In addition the effect of adrenergic drugs on the CP muscle was impressive Under light anesthesia methoxamine *injection resulted in spontaneous activity in the CP but not in the* thyro-pharyngeus portion of the inferior constrictor In addition this tonic activity was stronger than that produced by neostigmine

The classification of adrenergic receptors as alpha and beta was originally proposed by Ahl quist (1948) In the *present experiments,* phentolamine, an alpha-blocking agent, consistently inhibited the cricopharyngeal activity *induced by* methoxamine, an alpha-stimulator Further propanolol a beta blocking agent, did not inhibit this activity Moreover isoproterenol, which stimulates beta receptors, did not excite the CP muscle

*It would appear then that the CP is physio*logically different from the thyropharyngeus portion of the inferior constrictor and from the striated muscle of the tongue. However in 3 of 5 cats injected with gallamine, reflex ex citability in the CP stopped at the same time as that in the tongue musculature. In 2 other cats, reflex excitability lasted only about 3 *seconds longer in the CP muscle hardly a sig* nificant difference. This would indicate that the CP is not a completely involuntary muscle in all respects. Nevertheless, from observations with blocking and with stimulating agents, it appears that the receptor of the CP muscle is alpha adrenergic, that adrenergic fibers play *an excitatory role and that cholinergic fibers furnish background tonicity The two systems,* then do not act in opposition

SUMMARY AND CONCLUSIONS

The CP muscle was studied with adrenergic and cholinergic drugs, alpha and beta adren ergic blocking agents cholinergic blocking agents and neuromuscular blocking agents, *comparing its activity with that of the* thyropharyngeus and the tongue musculature

The CP exhibits characteristics of involuntary muscle with alpha adrenergic receptors, since

(1) *Only the* alpha-adrenergic drug excited *the muscle,* and only the alpha-adrenergic blocking agent inhibited this activity

(2) Beta-adrenergic drugs had no effect on its activity

(3) The thyropharyngeal part of the inferior

Acta

OTO LARYNGOLOGICA

SUPPLEMENT 310

DISTORTED SPEECH AUDIOMETRY

By

MARGARETA KORSAN BENGTSEN

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STOCKHOLM, SWEDEN

ACTA OTO-LARYNGOLOGICA

SUPPLEMENT 310

DISTORTED SPEECH AUDIOMETRY

A methodological and clinical study

By

Margareta Korsan-Bengtsen

GÖTEBORG 1973

To my son Jan

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To my son Jan

CONTENTS

"Nature has given men one tongue but two ears, that we may hear from others twice as much as we speak"
Epictetus

I Introduction

Modern audiometric methods enable diagnosis of hearing loss due to lesions of the middle ear cochlea or eighth nerve As a rule lesions central to the cochlear nuclei, i.e. in the central hearing pathways and auditory cortex are not demonstrable by conventional audiometry The anatomy of the hearing system, with each cochlea represented bilaterally in the auditory cortex, and with several commissural connections at different levels between the pathways of hearing implies a high intrinsic redundancy There is also superfluous information in the ordinary speech message which facilitates complete comprehension by normal subjects But full intelligibility of the message by patients with lesions involving the central hearing system, requires all available information in the speech signals.

Reduction of the information contained in the speech message by various forms of distortions challenges the integrative function of the hearing mechanism and reveals impairment of hearing. This was first shown by Bocca et al (1954 1955) who when testing patients with unilateral temporal lobe disorders used frequency-distorted speech. Using this test method they found a decreased discrimination by the ear on the opposite side of the lesion Several investigators have since used various forms of low-redundant or distorted speech tests and confirmed the original observation by Bocca and his group. (Matzker 1959 Lindén 1960, Jerger 1960 1970 Kimura 1961 de Quiros 1964 Maspétiol et al 1964 Lynn et al 1972 and others).

In a previous study (Korsan-Bengtsen 1968) five different forms of distorted speech tests were standardized and tried on patients with surgically verified lesions of the central hearing system as well as on a group of elderly persons. Preliminary results showed that distorted speech tests were of value in diagnosing lesions in the central hearing pathways and the auditory cortex. The clinical trial revealed that the test material required further improvement. It was also realized that further investigation of the effect of peripheral hearing loss on the test results of distorted speech audiometry was necessary as well as tests on larger series of patients with known anatomical lesions of the CNS. The aim of the present investigation was therefore threefold viz.

1) to devise and standardize a new Swedish normal test material for distorted speech audiometry in different age groups,

2) to evaluate the effect of peripheral hearing loss on the test results of distorted speech audiometry and

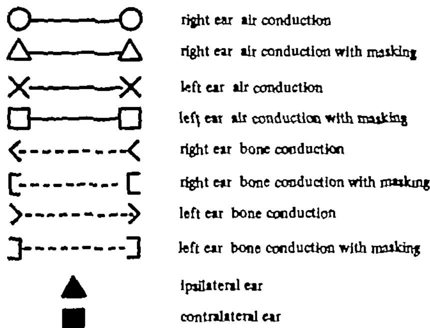
3) to analyse the results of distorted speech audiometry in patients with anatomically well-defined lesions in the central nervous system and to correlate the results with the site and extent of the lesions.

AUDIOLOGICAL TERMINOLOGY AND SYMBOLS

Speech reception threshold (SRT) is the sound intensity level at which the listener is capable of correctly repeating 50 percent of standardized Swedish spondee words.

Speech discrimination score is the percentage of correctly repeated words at the optimal speech sensation level – usually 30 dB above SRT

Speech sensation level (SL) is the sound intensity level above the actual SRT



STATISTICS

The statistical methods used in this study are described in "Nonparametric statistics for behavioral sciences" (Sidney Siegel 1956) and Documenta Geigy Wissenschaftlige Tabellen 6 Auflage

Mr Hans Wedel Fil lic. at the Department of Mathematics Chalmers University of Technology was consulted concerning the statistical analyses.

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I Introduction

Modern audiometric methods enable diagnosis of hearing loss due to lesions of the middle ear, cochlea or eighth nerve. As a rule lesions central to the cochlear nuclei, i.e. in the central hearing pathways and auditory cortex are not demonstrable by conventional audiometry. The anatomy of the hearing system, with each cochlea represented bilaterally in the auditory cortex, and with several commissural connections at different levels between the pathways of hearing implies a high intrinsic redundancy. There is also superfluous information in the ordinary speech message which facilitates complete comprehension by normal subjects. But full intelligibility of the message by patients with lesions involving the central hearing system, requires all available information in the speech signals.

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II Outlines of the anatomy of the central hearing pathways

It might not be out of place first to give a brief outline of the auditory pathways from the cochlea to the auditory cortex in the temporal lobe (fig. 1) The neuro-anatomic descriptions are taken from the studies by Jungert (1958) Roberts (1960) and Celesia et al (1969).

The cochlear nerve enters the brain stem at the lower border of the pons. It afterwards divides immediately into ascending and descending branches which run to the ventral and dorsal cochlear nuclei respectively

After synapsis in the cochlear nuclei the majority of the second order neurons cross over to the contralateral side and relay in the superior olivary complex or dorsal cochlear nucleus or join the lateral leminiscus. Some fibers from the ventral cochlear nucleus join the ipsilateral lemniscus after connections in the medial part of the olivary nucleus. The ascending fibers of the lateral lemniscus thus contain neurons of both the second and the third order and mainly from the contralateral cochlear nuclei. The ascending acoustic

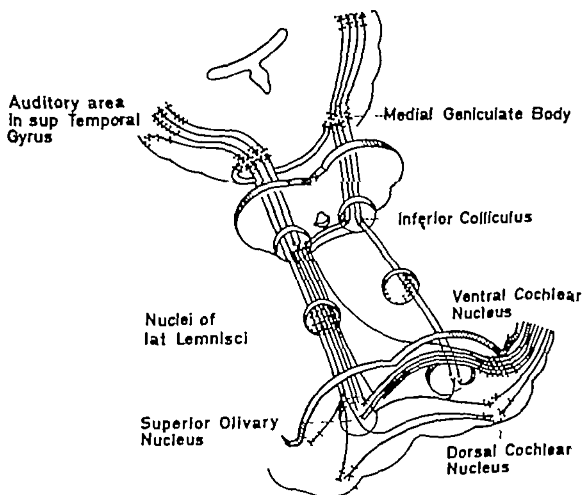


Fig. 1 The central auditory pathways A modification of J ngert s Auditory pathways in the brain stem"

pathway enters the inferior colliculus in the upper part of the brain stem and, after synapses, the fibers run rostrally to the medial geniculate body. There are commissural connections between the two colliculi and probably also between the medial geniculate bodies. The acoustic pathway then forms the so called "auditory radiation" which terminates in the temporal lobe deep in the Sylvian fissure.

Responses in man have been evoked (Celesia 1969) from a small area on the superior surface on the temporal lobe corresponding to the anterior and posterior transverse temporal gyri. This region represents the primary auditory cortex in man, and is schematic illustrated in fig. 2.

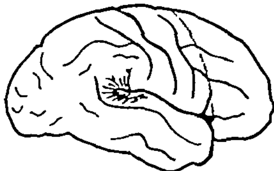


Fig. 2. Outline of auditory cortical area in man, obtained by evoked response (after Celesia and Roberts)

In this presentation the term central hearing disorders is used to designate changes in the hearing mechanism caused by lesions in the cochlear nuclei, the ascending hearing pathways and the auditory cortex.

III Speech audiometry in diagnosis of central hearing disorders Survey of the literature

Ordinary speech presents much more information to the listener than is necessary for normal perception Even if some speech sounds should not reach the auditory cortex owing to poor quality of the electroacoustic transmission system or functional impairment of the peripheral hearing organ or of the hearing pathways the remaining speech sounds would still be sufficient for normal discrimination The complicated anatomy of the hearing mechanism with both cochleas bilaterally represented in each auditory cortex and with numerous junctions at different levels of the pathways also contributes to guarantee good speech perception

Owing to this extrinsic and intrinsic redundancy ordinary speech discrimination tests generally fail to reveal local lesions of the auditory cortex or of the central hearing pathways. As early as 1928 Bunch showed that a whisper was heard equally well by a patient who had undergone total rightsided hemispherectomy as by a normal person This holds also for the perception of ordinary speech as has regularly been found in patients with lesions of the central hearing pathways and auditory cortex (Nylén 1939 Bocca et al 1954 1955 1963 Jerger 1960 de Quiros 1964 Korsan Bengtsen 1968 1970b and others)

Bocca et al (1954) were the first to demonstrate that a speech message that was made less redundant by frequency-distortion permitted normal discrimination in normals but a decreased performance by the contralateral ear in patients with unilateral destruction of the auditory cortex This approach to the problem has been used in many investigations which are surveyed below

Speech audiometry tests fall into two main groups monaural and binaural In monaural tests, words, sounds or signals are presented separately to one ear at a time and the recordings made on one side are compared with those obtained on the other In binaural tests both ears are tested simultaneously with equal or different words or signals The result is a summation of the hearing capacity in both ears and will probably be of central origin

MONAURAL SPEECH TESTS

Goldstein Goodman and King (1956) and Goldstein (1961) used a relatively difficult verbal material consisting of indistinctly pronounced PB-words in the examination of 4 patients before and after left-sided hemispherectomy With this (Rush Hughes test) they found a difference of 25% in discrimination between the ipsi and contralateral ear compared with 9% with the ordinary PB-lists. Goetzinger (1972) obtained similar results with Rush Hughes test in patients with central auditory lesions

Frequency-distorted speech

Speech signals can be made low redundant by means of electronic filters which attenuate parts of the frequency spectrum. The discrimination of filtered speech varies considerably with the type of filters used, i.e high pass, low pass or band pass filters as well as with the verbal material

Normal persons can manage fairly large reductions in the frequency spectrum of speech signals before any decrease occurs in the discrimination scores. With a low pass filter with cut-off frequency around 800 Hz or band pass filters with the same rejection of frequencies the intelligibility of sentences is 70–90% at 35–50 dB sensation level (Hirsh 1954 Bocca 1954 1955 Lindén 1960 Maspétiol et al 1964 and Korsan Bengtsen 1968 1970a).

The most important frequencies of speech material such as CVC nonsense syllables and PB-words range from 1500 to 2500 Hz (French and Steinberg 1947 Pollack 1948 and Hirsh 1954)

The use of band pass filters in the low frequency area usually result in somewhat higher discrimination scores than low pass filters within the same frequency range This is because of a masking

effect of the most low frequency sounds in low pass filtered speech (Palva 1965).

Bocca, Calearo and Cassinari (1954) were the first to show that a patient with a right-sided temporal lobe tumour achieved a lower score for filtered speech on the ear opposite to the lesion. Disyllabic meaningful PB-words were used as test material filtered through a low pass filter with a cut-off frequency of 800 Hz. The score for the contralateral ear was reduced by 20–25% compared with that for the ipsilateral ear. In a follow-up study the authors demonstrated the general validity of their original finding by the test results for filtered speech in 18 patients with unilateral temporal lobe disorders. In those cases, where the test results were equal for both ears, surgery confirmed that the tumour had not destroyed the auditory cortex. Bocca and his group thus showed that distorted speech was useful in the exploration of the cortical auditory function.

Bocca (1958) and Calearo and Antonelli (1963) continued their research in filtered speech. Using a low pass filter with a cut-off frequency of 500 Hz they found that the discrimination scores for the contralateral ear in patients with unilateral temporal lobe lesions were reduced by 20–40%. This reduction in perception of filtered speech was the same whether the right or left hemisphere was involved.

Antonelli and Calearo (1968) studied 11 patients with right-sided temporal lobe epilepsy with the filtered speech test before and after surgery. They invariably found a reduced performance with filtered speech whether Heschl's gyrus had been removed or not. They felt that this reduction was due to the disease or surgery with secondary defects in the auditory function in spite of the absence of anatomical changes in auditory cortex, or to the existence of some secondary auditory area enclosing the primary auditory cortex.

Filtered speech tests for diagnosing temporal lobe disorders have thus been widely used (Lindén 1960, Jerger et al 1960, 1964, Maspétiol 1964, Berlin et al 1965, 1972, Korsan-Bengtsen 1968, 1970b and Lynn et al 1972) and the results are in agreement with those reported by Bocca et al.

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The results obtained with filtered speech tests in brain stem lesions vary more than in patients with cortical disease. Calearo and Antonelli (1968) investigated 24 cases with brain stem lesions. 8 had tumours and 16 had lesions due to multiple sclerosis, infections or vascular disorders. Of 23 tested with filtered speech, 8 showed a monolateral deficit, and 4 a bilaterally reduced score. In 7 patients with brain stem lesions Jerger (1964) found a 24% difference in the discrimination score between the homo- and contralateral ear for low pass filtered speech.

Flowers and Costello (1963) investigated low pass filtered speech (960 Hz) in children with speech-articulation deficiencies and found the score to be significantly lower than in normal children. The results suggested that speechretarded children might have changes in the central hearing mechanism.

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It is interesting that administration of scopolamine and atropine which have a depressive action on mental performances, markedly reduces the perception of filtered speech in young subjects (Calearo and Antonelli 1964).

Interrupted speech

Speech can be periodically interrupted by an electronic switch, which causes amplitude-modulations of the speech waves (see part IV). In this way parts of the speech message are cancelled. The effect of periodically interrupted speech on discrimination has been investigated in normals by

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among others Miller and Licklider (1950) Bocca 1958 Calearo and Antonelli (1963) and Teatini (1970a). The discrimination was found to depend on the number of interruptions per second (int/sec) as well as the ratio between the duration of the periods of speech and that of the intervals. When the interruption rate is increased from 1 to 10 000 the discrimination score is increased from around 50% to 85% at 10 int/sec. Any further increase in the interruption rate has only little effect on the score Teatini (1970) found some what higher scores at 10 int/sec probably because sentences were used as test material instead of PB-words, which suffer very quickly by various forms of distorsion.

If periodically interrupted speech is presented to patients with unilateral temporal lobe disorders, the discrimination score will be reduced on the side opposite the lesion as shown by Bocca (1958) Calearo and Antonelli (1963) and Antonelli (1970c). The score is 15–25% lower than that for the ipsilateral ear whether the lesion is right or leftsided. This reduced performance with interrupted speech was also evident in patients brain stem lesions, where one or both ears showed a poor discrimination score (Bocca 1963 1967) Calearo and Antonelli (1968)

Similar results in brain stem lesions have been reported by Jerger (1970c) who used varying speech-time fractions with synthetic sentences.

Bocca (1958), Kirikae (1964) and Antonelli (1970a) tested the effect of periodical interruptions of speech on elderly persons with normal hearing for age They found that the discrimination scores were strongly reduced in this group compared with that in young subjects. The difference in perfor mance was ascribed to degenerative changes in the central hearing pathways and auditory cortex.

The effect of drugs on the performance in tests with interrupted speech is noteworthy Calearo and Antonelli (1964) showed that 1 mg of scopolamine markedly depressed the discrimination score in young test subjects, while atropine and barbiturates did not

In difficult tests, as in interrupted speech the discrimination score might vary with the test subject s intelligence Bocca (1967) and Teatini (1970a) were able to demonstrate a correlation between the intelligence quotient (IQ) and the performance of interrupted speech tests the discrimination score varying with IQ

Time-compressed speech

The intelligibility of a verbal material as a function of an increased speech rate has been investigated extensively (Garvey 1953 Calearo and Lazzaroni 1956 Fairbanks et al 1957 de Quiros 1964 and Korsan-Bengtsen 1968 1970a).

The normal speech rate ranges from 110–140 words/minute (wpm) according the habit of the speaker and the language used Speech can easily be speeded by increasing the playback speed of an ordinary tape-recorder and the effect on the speech will be both a change in the rate and a frequency shift of the speech sounds. Using this method Garvey (1953) showed that the intelligibility of spondee words decreased to 65% at an acceleration of 2 0 and this score was reduced to only 10% when the acceleration was increased further to 2.5 Sentences are affected less by time-frequency distorsion and were almost 90% intelligible at a time-compression of 0 67 as shown by Klumpp and Webster (1961) Fairbanks et.al. (1957) obtained similar results for connected discourse with varying speech rates.

The speech-rate can also be increased without any change in the frequency spectrum. Such speeded speech can be obtained either by quick reading of the verbal material or by use of a special tape recorder with a group of rotating playback heads. With this special tape recorder the speech rate can be altered from 0 5–2 0 T When the speech rate is in reased the intensity has to be increased in order to maintain the same intelligibility Calearo and Lazzaroni (1957) thus found that at a speed of 350 wpm there was a threshold shift of 10–15 dB in normals. The discrimination curves kept their shape but were displaced to the right Similar results have been obtained by de Quiros (1964) and Korsan-Bengtsen (1968 1970a) in normals.

The effect of time-compressed speech has also been studied in patients with lesions involving the central hearing pathways and auditory cortex Thus, Calearo and Lazzaroni (1957) Bocca (1958) Bocca and Calearo (1963) de Quiros (1964) and Korsan Bengtsen (1968 1970b) found that localized lesions in the auditory cortex significantly reduced the score achieved by the contra lateral ear for time-compressed speech

Patients with diffuse CNS lesions including those with associated increased intra-cranial pressure generally show a bilateral decrease in

discrimination of time-compressed speech.

Calearo and Antonelli (1968) also studied the effect of time-compressed speech in patients with brain stem lesions and found a decrease in discrimination in 14 out of 23 cases. The loss was mainly unilateral. By administration of barbiturates to young subjects, Antonelli and Calearo (1968) found a significant decrease in perception of time-compressed speech, probably as a result of depression of the reticular formation in the brain stem. Drugs such as scopolamine and atropine had no such effect on the results of the test.

Aged people sometimes achieve a reduced score for time-compressed speech (de Quiros 1964, Korsan-Bengtsen 1968, Antonelli 1970a and Schon 1970) and the reduced performance has been interpreted as a result of degenerative changes in the CNS. It is interesting to note that administration of amphetamine – like drugs to elderly patients significantly improves discrimination of time-compressed speech (Blondum and Bocca 1959).

BINAURAL SPEECH TESTS

If normal speech is presented to both ears simultaneously (di-otic hearing) the discrimination score is higher than when it presented to only one ear (monaural listening). Utilizing this binaural gain, Groen and Hellema (1960) investigated monaural and binaural speech perception in hard-of hearing children. They found that in the presence of peripheral lesions the curve for binaural articulation was much steeper than that for monaural articulation and that the gain in SRT was 9 dB. In children with central deafness the difference between binaural and monaural discrimination did not vary much. This shows that an intact central auditory function is necessary for securing binaural summation of the speech.

If the speech material is made more refined and difficult it is possible to devise more specific tests for central hearing disorders. Bocca (1955) presented speech at a very low intensity to one ear and the same speech, sufficiently intense but low pass filtered, to the other ear. The monaural discrimination did not exceed 50% in either ear. When this speech was delivered simultaneously to the ears, Bocca found that the binaural discrimination was approximately equal to the sum of the monaural scores. This test thus provided a summation or integration of two low-redundant messages.

Calearo (1957) used this binaural test in patients with temporal lobe disorders. He found there was no summation if the low-intensity speech was delivered to the ear opposite the lesion. By reversing the presentation of the stimuli, the patients received a satisfactory binaural summation and the test method could thus be used in the diagnosis of central hearing disorders.

Jerger (1960) used the same testing technique in patients with lesions of the auditory cortex. He showed that the discrimination score was decreased for both types of speech when delivered to the contralateral ear. The binaural summation in either combination was a little better than the score for the ipsilateral ear alone.

That the brain can combine or synthetize incomplete speech sounds from the two ears to a meaningful message was first shown by Arnold (cited by Fletcher 1953). He used low pass filtered speech to one ear (cut-off frequency 1000 cps) and the same test words but high pass filtered to the other ear (same cut-off frequency). Monaural discrimination was very low while binaural listening permitted good discrimination.

The same principle with two incomplete messages to test the central synthetic hearing function was also used by Matzker (1959). To one ear he presented low pass filtered speech (narrow band 500–800 cps) and to the other ear the same speech but high pass filtered (narrow band 1815–2500 cps). The speech information from one band alone was too scanty to warrant more than a 25–30% discrimination score. Delivered binaurally to normals there was good integration of the two fractions and they achieved maximum score by this test. Matzker found that the binaural test showed decreased discrimination score in 80% of all patients with brain tumours. Also patients with cerebral atrophy of varying origin, multiple sclerosis and skull injuries showed an increased number of errors in this test, as also in brain stem lesions. The study of Hall (1965) supports this finding in brain stem lesions, as he found that the middle superior olive participates in two click lateralization. Similar findings with binaural filtered speech in temporal lobe lesions were also made by Tillman, Bocy and Carhart (1966).

The same method, with two incomplete filtered speech material presented to each ear was also

investigated by Lindén (1960) The bands used were low pass filter 640" and high pass filter "2000" or "2000x2" When these bands were tested binaurally Lindén could not show that the binaural discrimination score was inferior to the frequency – distorted monaural speech in patients with an expanding intracranial lesion Similar observations are also made by Ohta et al (1967) in the binaural fusion test in patients with brain tumours. Matzker s findings concerning binaural synthesis in central hearing disorders could thus not be proved

Feldman (1964 1967) presented dissimilar three syllabic words at high intensity levels simultaneously to both ears. Young normal subjects achieved 100% discrimination score in both ears in this dichotic listening situation. Patients with diffuse central lesions had decreased discrimination bilaterally without any difference between the ears. In local lesions of the central hearing pathways perception by the ipsilateral ear was reduced when the brain stem was injuried while patients with lesions above the colliculus inferior achieved only a reduced score for the contralateral ear

A similar type of competitive speech audiometry was used by Kimura (1961a b) Pairs of digits were presented either simultaneously to both ears or alternatively to the right and the left ear In patients who had undergone left or right sided temporal lobectomy she found a significant loss in the contralateral ear on simultaneous presentation to both ears whereas frontal lobectomy had no such effect Damage to the left temporal lobe was found to impair the over-all performance in this test both pre- and postoperatively more than right sided lesions. These results suggest that both auditory cortices take part in discrimination and that the left temporal lobe is particularly important in perception of speech material

Similar results were obtained by Milner (1965) and Oxbury and Oxbury (1969) on patients who underwent temporal lobectomy because of epileptic seizures.

A similar test method with spondee words in dichotic listening was devised by Katz (1962 1963 1968). The test words were presented in a partially overlapping fashion so that the last part of one spondee word was heard simultaneously with the first part of the following spondee word With this method there was competitive stimulus presented to the ears. Katz showed that patients with lesions in cortical and subcortical areas made an increased number of mistakes by the contralateral ear In peripheral sensorineural hearing loss there was bilateral reduction of the discrimination score By shortening the score achieved with the percentage of errors made in PB-word discrimination it was possible to evaluate the degree of involvement caused by central hearing disorders in these cases. In patients with lesions in the hearing pathways and auditory cortex Jerger (1964) found that the discrimination score for PB-words given by ear phones was reduced when sentences were presented simultaneously to the other ear as competition Lesions in other parts of the brain had no such effect This test method is thus suitable for exploring disturbances in the central auditory system

Swinging speech

If a verbal material is periodically switched from one ear to the other so that each ear receives half of the message normal subjects will achieve a discrimination score of 90–100% at any switching rate as shown by Bocca (1961 1963) The same results are also obtained in patients with isolated lesions of the auditory cortex (Bocca and Calearo 1963) while in patients with lesions in the brain stem the discrimination curve falls abruptly at a switching rate of 3–8 int/sec. (Calearo and Antonelli 1968) Nine out of 22 patients with brain stem lesions scored low in the swinging speech test while the others achieved a normal score This finding in brain stem lesions is explained by a disturbance in the fusion of two separate monaural messages at the level of the crossing of the auditory pathways.

Cherry and Taylor (1954), on the other hand found this "dip" in normals at a switching rate around 4 int/sec. and they attributed this reduction in discrimination score to a mental delay due to a switch in attention from one ear to the other At higher interruption rates discrimination was again normal

IV Methodological part

SPEECH MATERIAL USED FOR DISTORTED SPEECH TESTS

The function of auditory cortex is to integrate the incoming sound patterns to a meaningful message to the listener. Speech thus should be the ideal test material in the evaluation of disorders of the central hearing mechanism. For detecting central hearing lesions the speech material should preferably be influenced as little as possible by defects in peripheral hearing. As is well known, the discrimination of short words, such as PB-words, is easily impaired by end organ lesions and still more by nerve fiber deafness (Licklider and Miller 1951, Lidén 1954, Schuknecht 1955, 1958, Walsh and Goodman 1955, Goodman 1957 and others).

The intelligibility of sentences depends on their meaning and the context, and they are thus more resistant to changes in the peripheral hearing mechanism than are words (Jerger 1970b, Teatini 1970b). Sentences also provide a better basis for different forms of distortions than do short words. A disadvantage of sentences is that they can be easily remembered in repeated tests. This can be avoided by using a sufficient number of sentences in each test.

The speech test material which had been used in earlier investigations (Korsan-Bengtsen 1968) for the diagnosis of central hearing disorders had appeared to vary in intelligibility and not to be comprehensive enough.

A new speech test material consisting of 500 sentences was therefore designed. The length of each sentence varied between 4 and 8 words. Difficult and uncommon words were avoided to prevent the influence of intelligence and educational level of the listener.

The test material was recorded on a magnetic tape by a trained male speaker. This speech material, after being recorded, was the master tape. The recording was performed in a sound proof room. A microphone AKG MD 421 and a dual channel Revox A 77 tape recorder were used. The frequency response characteristics of the equipment were checked before recording and was found to be in agreement with the technical data. The new speech test material was then standardized and calibrated on normal hearing subjects to reach the same intelligibility of each sentence. As shown by Harris (1948) the slope of the discrimination curve is much steeper when the intelligibility of the test material is taken into account compared with equal intensity of the test words.

As this new material was intended to be presented at a sensation level of 30–35 dB, it was desired to calibrate the sentences so as to produce a discrimination curve with a very steep rise as a function of intensity, approaching around 100% discrimination score already at 10–15 dB above the tone threshold. The observation of a subnormal discrimination score should thus not be ascribed to insufficient intensity of the speech, but to other factors of the hearing function of the listener.

Thus, the 500 sentences were tested on 5 young students with normal hearing. The presentation of each sentence started 5 dB below the tone threshold, and the intensity was then increased 1 dB at a time by a special attenuator until the whole sentence was repeated correctly. The mean level was then calculated for each sentence. The mean level of all sentences was 19.8±1.7 dB re 2×10^{-5} N/m^2. The master tape was then replayed, and the level of each sentence was increased or decreased in order to reach the same intelligibility of the test material.

The material of sentences was then divided into 20 lists, each consisting of 25 sentences. As each sentence, independent of its length, contained 4 key words, the maximum discrimination score for each list would thus be 4x25 = 100%. The key words were both mono bi- and polysyllable.

Lists 9–20 were submitted for periodical interruptions of speech with three different rates of

interruption (see side 16). Lists 1–8 were submitted for time-compression of speech. First, a new recording was made of these 8 lists whereby the speaker accelerated his speech from normally 130 wpm to around 190 wpm without any change in his articulation. This speeded speech was then used for further time-compression (see side 19) by means of a special tape recorder.

The test material also included 4 lists nr 21–24 which were submitted for frequency distorted speech. Each list contained 17 sentences, and the lists had been composed by the Director of the Audiopedic section Dep of Audiology Sodersjukhuset Stockholm. The recording of these lists had been made earlier by a trained male speaker. A Ferrograph tape recorder and a microphone M 221 A were used after control that their technical performance were in agreement with assigned data.

As an additional test a competing speech test was recorded. SPB-list nr 21 (Lidén 1954) containing 50 phonetically balanced words with a carrier phrase was recorded on one channel and lists nr 9 and 10, together 50 sentences on the other channel in such a way that each sentence covered both the test word and the carrier phrase. The recording equipment was a Revox A 77 tape recorder and the microphone used was AKG MD 421. A male speaker was used for both recordings in order to avoid differences in voice quality from influencing the discrimination of the test words.

DISTORSIONS INTRODUCED

Periodical interruption of speech

Twelve lists, nr 9–20 of the recorded and adjusted speech material were fed into an electronic interrupter triggered by a Wavetec function generator. In this way the speech signals were periodically interrupted by rectangular amplitude modulations which resulted in a sequence of short speech samples alternating with silent intervals. When the interrupter turned the signal off the intensity of the speech signals was reduced by approximately 80 dB. After having passed the interrupter the distorted speech message was recorded on a Revox A 77 tape recorder. The principal equipment for producing periodically interrupted speech is shown in a block diagram in fig. 3 as is a schematic illustration of the effect on the undistorted speech signals by amplitude modulation.

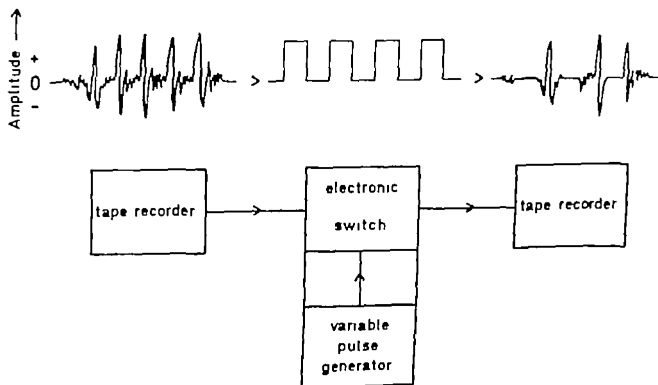


Fig. 3. Block diagram of the equipment used in periodic amplitude modulation of speech



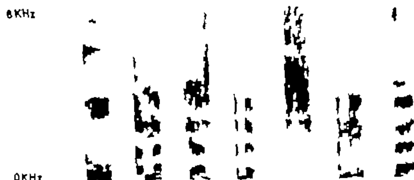


Fig. 4. Sonagram of one of the test sentences before and after amplitude modulations of the speech.

Three rates of interruptions were used, viz 10 7 and 4 int/sec and with a constant speech-time fraction of 0 5

The lists 9–12, containing 100 sentences, were used for the interruption rate of 4 int/second This rate gave duty time of 125 msec of the speech signal

The lists 13–16 with 100 sentences together were used for the interruption rate 7/second. With this rate the speech message was on for about 70 msec

Finally the lists 17–20 containing 100 sentences, were used for the interruption rate 10/second, and the on-time for the speech signals was 50 msec

The recording of the interrupted speech was stored as a master tape and two copies were made for clinical use

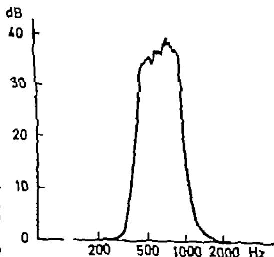


Fig. 5a. Frequency characteristics of 3 band pass filters used, with center frequencies 500 640 800 Hz.

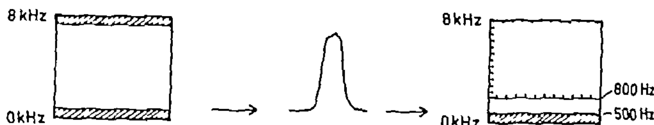




Fig 5b. Schematic illustration of the equipment used in frequency-distortion of speech.

8 KHz



HU N DEN BLE VRA DD O G O M DE S E J

8 KHz



0KHz

Fig 6. Sonagram of one of the test sentence before and after frequency-distorsion

Sonagrams were made from the original tape and from the same speech material after distortions had been *introduced*. *An illustration is given* in fig. 4.

Frequency – distorted speech

Four lists (nr 21–24) consisting *of all together* 68 sentences, were submitted for frequency – distortion of the speech message.

The recorded test material was fed into three band pass filters, coupled in parallel, model Brüel & Kjaer. Each filter was 1/3 octave wide and center frequencies of the filters were 500 Hz, 640 Hz and 800 Hz, respectively. The attenuation of the coupled filters was 40 dB/octave and the attenuation characteristics of these filters are given in fig. 5a. *After having passed the filters* the frequency – distorted speech lists were recorded on another Revox A 77 tape recorder. Two copies *for clinical use* were made from this master tape. The equipment for frequency – distortion is shown in the block diagram in fig. 5b. As illustration of the effect on speech by band pass filtration, sonagrams were made from the original tape and from the same speech message after frequency – distortion (fig. 6).

Time – compression of speech

Eight lists, nr 1–8 were submitted for time compression of the speech. As mentioned earlier the speaker had speeded his speech rate on these lists to around 190 wpm. In order to increase the speed further *the lists were fed into a Tempophon* tape recorder. With this tape recorder the speed of the tape could be changed by means of four movable playback heads from 0.5 T to 2.0 T without any change in the frequency spectrum.

The time-compression of the lists were carried out at the Royal Institute of Technology, Stockholm. The lists 1–4 all together 100 *sentences*, were submitted for the fastest speed, giving a speech rate of around 290 wpm, corresponding to

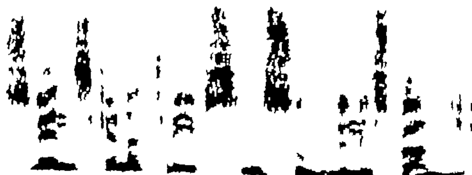




Fig. 7. Sonagrams of one of the test sentences before and after time-compression.

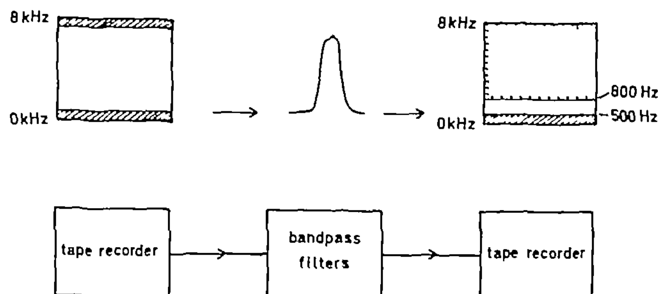


Fig. 5b. Schematic illustration of the equipment used in frequency-distortion of speech

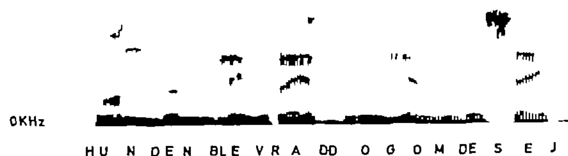




Fig. 6. Sonagrams of one of the test sentences before and after frequency-distortion

materials and were asked to repeat each sentence as correctly as possible. Between each test round, which lasted about 30 minutes, there was a short pause to avoid inattention due to fatigue.

Test methods

Before the tests were started the pure tone hearing threshold was recorded on each ear. Taped spondee and SPB-words (Lidén 1954) were used for ordinary determinations of the speech reception thresholds and discrimination scores for each test subject.

The distorted speech tests were presented monaurally with exception for the competing speech test which was presented in a dichotic way.

Monaurally presented lists

In *material I* the 4 lists within each test, all together 24 lists, were presented in a consecutive test order. The test subjects were allowed to choose which ear they wished to start with, and after finishing a list, there was a shift over to the other ear. Thus, in each test two lists were always presented to the right ear and two to the left.

The first 5–6 sentences in each list were presented at a sensation level of 35 dB. Thereafter the intensity was decreased stepwise after each fifth sentence until the discrimination score dropped to 0–20%.

In *material II* the test method was changed, so that the 4 test lists within each test all together 24 lists, were presented in a randomized order giving twenty-four combinations of the test sequence. Each test list was also devided into 4 parts, and each part was tested at one of the intensities 0, 10, 20 and 35 dB sensation level. One exception was frequency – distorted speech where 0 dB sensation level was excluded. The order of the intensity levels was also randomized. Both the test sequence between the lists and the intensity sequence for each list were distributed by envelope technique and remained the same through all tests. No test was started at 0 dB sensation level. As a compensation for these six intensity combinations thus discarded six other randomized combinations were added. Two lists were always presented to the right ear and two to the left ear.

In *material III* only the first two lists in each test were presented, and at a sensation level of 35 dB. The test order between the right and left ear was randomized, as was the test order between the two lists.

The test method in *material IV* was exactly the same as for material III. The different tests were always presented to the test subjects in the same order namely with interrupted speech tests first, then frequency – distorted speech, and as the last test time – compressed speech.

Binaural test

The competing speech test was examined on 15 of the test subjects in material III. The SPB-words were presented at 40 dB sensation level to one ear and the competing sentences to the other ear at a sensation level of 50 dB. The test subjects were instructed to ignore the sentences heard on one side and repeat only the SPB-words heard by the other ear. 25 SPB-words were presented to each ear and the test order between the right and left ear was randomized.

RESULTS

Monaural tests

The discrimination scores were calculated relative to the number of correct repeated key-words in each sentence. The mean discrimination scores and standard deviations were calculated for each test list at different sensation levels, as was the sum mean value and standard deviation for each test.

The results obtained in material I with 45 young test subjects, are given in fig. 8 and 9. As can be seen, the mean scores exceeded 90% in all tests at a sensation level of 35 dB except for the test with 4 int/sec. It is also evident that the first list in the test with 4 int/sec. had a lower score than the three other lists in this test. The same observation, although not so pronounced was found in frequency – distorted speech.

The results obtained in material II where the test sequence of the lists and the intensity of the speech were randomized, are given in fig. 9 and tables I–VI.

The results for the test lists within each test, irrespective of their test order showed that the mean discrimination scores were fairly close to each other at a sensation level of 35 dB. At lower intensities the deviations of the mean discrimination scores and standard deviations were larger as

T = 0.46. The lists 5–8 containing together 100 sentences, were submitted for a moderate time compression, with a received speech rate of around 220 wpm corresponding to T = 0.58. The speed of the speech was calculated by feeding the original and time-compressed speech into a Brüel/Kjaer logaritmic recorder type 2305. The time for each sentence was measured with 1 decimal. The total time required for each list excluding the pauses between the sentences was then calculated.

In this way the number of words per minute (wpm) and the value of T could be computed. After time-compression two copies of the master tape were made for clinical use. In order to illustrate the effect of time-compression on the speech message sonagrams were made from the original tape and from the same speech material after time-compression (see fig. 7).

STANDARDIZATION OF THE TESTS AND TEST METHODS

The purpose of this section was to elucidate the discrimination scores of the new distorted speech material in normals of different ages. The test battery consisted of seven tests:

1) interrupted speech with 10 int/sec. 4 lists, nr 17–20 were used with 25 sentences in each list.

2) interrupted speech with 7 int/sec. 4 lists, nr 13–16 were used with 25 sentences in each list.

3) interrupted speech with 4 int/sec. 4 lists nr 9–12 were used with 25 sentences in each list.

4) frequency – distorted speech. 4 lists nr 21–24 were used with 17 sentences in each list.

5) time-compressed speech I with a speech rate around 220 wpm. 4 lists, nr 5–8 were used with 25 sentences in each list.

6) time-compressed speech II with a speech rate around 290 wpm. 4 lists, nr 1–4 were used with 25 sentences in each list.

7) competing speech test. 2 lists with 25 SPB words in each list were used. As competing message sentences were presented simultaneously.

At the beginning of each list a tone of 440 Hz was recorded for calibration purposes. The level of the tone was adjusted to –5 dB on the VU-meter which corresponds to a sound pressure level of 22.0 dB re 2×10^{-5} N/m²

Equipment

The prerecorded speech materials (see side 16) were presented to the test subjects who were wearing earphones via a dual channel Revox A 77 tape recorder, the output of which fed a Madsen or Camplex speech audiometer. Earphones THD 49 Mx 41 AR were used. All tests were performed in sound proof rooms. A Camplex or Madsen tone audiometer was used for determining the tone threshold. These audiometers as well as the earphones, were calibrated according to ISO-standard (1964).

Test subjects

Four groups of test subjects were chosen for standardizing the 7 new types of test material and to determine the performance – intensity curves for the different tests. The criteria for acceptance as a test subject for taking part in the test were that the tone audiogram did not exceed 5 dB at any of the frequencies 250–2000 Hz on both ears, and that the speech reception threshold for the young test subjects did not exceed 5 dB on either ear.

Material I. 45 subjects. 23 women and 22 men. The mean age was 24±4 years (range 17–32 years).

Material II. Another group consisting of 20 subjects, 9 women and 11 men. The mean age was 24±4 years (range 18–34 years).

Material III. Another group of 20 subjects, 11 women and 9 men. The mean age was 26±3 years (range 19–34).

Material IV. 20 subjects, 12 women and 8 men 50–60 years old (55±3.5 years). The mean tone threshold was 5.1±4.2 dB. The mean hearing loss at 4 kHz was 20±14 dB. The mean speech reception threshold for spondees was 7.1±3.3 dB (a hearing level of 0 dB for spondee words correspond to 22.0 dB re 2×10^{-5} N/m²).

The reason why material IV was included for standardizing purposes was that some of the patients with central hearing disorders would probably be elderly.

Instructions

As this distorted speech material sounds unfamiliar to the listener all test subjects were thoroughly informed about the type of distorsions in the test

Tables I–VI.
Mean discrimination scores and standard deviations obtained by 20 young subjects on distorted speech tests, presented at different sensation levels. The results are analysed according to the test sequence of the lists.

Table I Interrupted speech, with 10 int/sec.

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	–	97.1	97.0	98.2	93.2	96.9
	SD	5.0	5.4	3.4	7.3	5.5
	SEM	1.1	1.2	0.8	1.6	0.6
20	–	91.2	91.2	93.6	94.2	90.1
	SD	8.5	14.3	9.1	9.4	11.1
	SEM	1.9	3.2	2.0	2.1	1.2
10		60.2	67.9	68.4	4 8	67.8
	SD	18.6	21.6	19.2	25.0	21.5
	SEM	4.2	4.8	4.3	5.6	2.4
0		11.9	12.9	9.4	19.2	13.4
	SD	23.5	13.0	12.1	23.2	18.7
	SEM	5.2	2.9	2.7	5.1	2.1

Table II Interrupted speech, with 7 int/sec

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35		92.3	95.2	97.1	95.5	95.0
	SD	10.0	7.5	4.9	7.3	7.7
	SEM	2.2	1.7	1.1	1.6	0.9
20		92.5	90.4	93.3	91.5	91.9
	SD	10.0	13.6	7.9	11.6	10.8
	SEM	2.2	3.0	1.8	2.6	1.2
10		58.4	65.0	60.0	72.5	64.0
	SD	23.6	24.8	21.9	25.4	24.1
	SEM	5.3	5.5	4.9	5.7	2.7
0		12.1	14.6	11.0	14.8	13.1
	SD	12.5	15.8	12.2	16.0	14.1
	SEM	2.8	3.5	2.7	3.6	1.6

Table III Interrupted speech, with 4 int/sec

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35		80.0	80.4	81.6	78.6	80.2
	SD	19.6	17.8	15.9	15.4	16.5
	SEM	4.4	4.0	3.5	3.0	1.8
20		69.3	72.5	67.5	74.4	70.9
	SD	24.7	14.8	18.7	17.6	19.1
	SEM	5.5	3.3	4.2	3.9	2.1
10		41.7	50.4	49.0	56.7	49.5
	SD	20.6	24.2	21.4	25.7	23.3
	SEM	4.6	5.4	4.8	5.8	2.6
0		11.3	16.3	10.8	17.7	14.0
	SD	14.8	23.3	14.5	23.4	19.4
	SEM	3.3	5.2	3.2	5.2	2.2

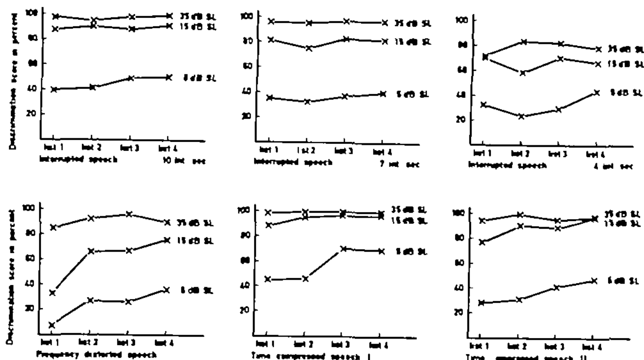


Fig. 8. Mean discrimination scores achieved by 45 young test subjects in 6 different forms of low-redundant speech tests. The 4 lists within each test are presented in numerical order.

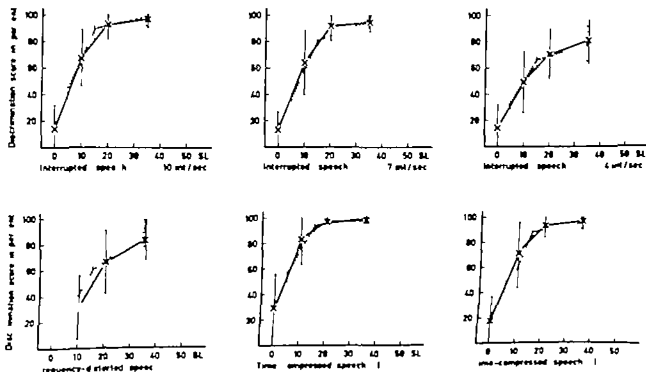


Fig. 9. Mean discrimination scores and standard deviations on 4 lists within each test scored by 20 and 45 young subjects respectively. Continuous lines result from 20 subject. Dotted lines result from 45 subject.

Tables I–VI.
Mean discrimination scores and standard deviations obtained by 20 young subjects on distorted speech tests, presented at different sensation levels. The results are analysed according to the test sequence of the lists.

Table I Interrupted speech, with 10 int/sec

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	x̄	97.1	97.0	98.2	95.2	96.9
	SD	5.0	5.4	3.4	7.3	5.5
	SEM	1.1	1.2	0.8	1.6	0.6
20	–	91.2	91.2	93.6	94.2	90.1
	SD	8.5	14.3	9.1	9.4	11.1
	SEM	1.9	3.2	2.0	2.1	1.2
10		60.2	67.9	68.4	74.8	67.8
	SD	18.6	21.6	19.2	25.0	21.5
	SEM	4.2	4.8	4.3	5.6	2.4
0	–	11.9	12.9	9.4	19.2	13.4
	SD	23.5	13.0	12.1	23.2	18.7
	SEM	5.2	2.9	2.7	5.1	2.1

Table II Interrupted speech, with 7 int/sec

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	x̄	92.3	95.2	97.1	95.5	95.0
	SD	10.0	7.5	4.9	7.3	7.7
	SEM	2.2	1.7	1.1	1.6	0.9
20		92.5	90.4	93.3	91.5	91.9
	SD	10.0	13.6	7.9	11.6	10.8
	SEM	2.2	3.0	1.8	2.6	1.2
10		58.4	65.0	60.0	72.5	64.0
	SD	23.6	24.8	21.9	25.4	24.1
	SEM	5.3	5.5	4.9	5.7	2.7
0		12.1	14.6	11.0	14.8	13.1
	SD	12.5	15.8	12.2	16.0	14.1
	SEM	2.8	3.5	2.7	3.6	1.6

Table III Interrupted speech, with 4 int/sec

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35		80.0	80.4	81.6	78.6	80.2
	SD	19.6	17.8	15.9	15.4	16.5
	SEM	4.4	4.0	3.5	3.0	1.8
20		69.3	72.5	67.5	74.4	70.9
	SD	24.7	14.8	18.7	17.6	19.1
	SEM	5.5	3.3	4.2	3.9	2.1
10		41.7	50.4	49.0	56.7	49.5
	SD	20.6	24.2	21.4	25.7	23.3
	SEM	4.6	5.4	4.8	5.8	2.6
0		11.3	16.3	10.8	17.7	14.0
	SD	14.8	23.3	14.5	23.4	19.4
	SEM	3.3	5.2	3.2	5.2	2.2

Table IV Frequency-distorted speech.

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	x̄	71.7	86.0	88.1	90.2	84.0
	SD	18.1	13.3	11.8	11.2	15.4
	SEM	4.1	3.0	2.6	2.5	1.7
20	x̄	60.9	62.3	68.1	75.7	66.8
	SD	24.6	26.9	23.5	22.6	24.7
	SEM	5.5	6.0	5.2	5.0	2.8
10	x̄	24.9	27.7	36.5	39.2	32.1
	SD	21.6	24.5	24.7	29.1	25.4
	SEM	12.5	5.5	5.5	6.5	2.8

Table V Time-compressed speech, with 220 wpm

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	x̄	98.9	98.7	98.9	98.6	98.8
	SD	3.3	3.3	2.9	2.7	3.0
	SEM	0.7	0.7	0.6	0.6	0.3
20	x̄	97.3	98.3	94.2	97.3	96.8
	SD	4.1	2.8	8.3	5.3	5.6
	SEM	0.9	0.6	1.9	1.2	0.6
10	x̄	83.5	83.4	81.4	84.8	83.3
	SD	17.7	21.6	18.5	19.2	19.0
	SEM	3.9	4.8	4.1	4.3	2.1
0	x̄	24.0	29.6	29.4	35.6	29.7
	SD	26.8	26.7	24.2	30.9	27.1
	SEM	6.0	6.0	5.4	6.9	3.0

Table VI. Time-compressed speech, with 290 wpm

SL		first tested list	second tested list	third tested list	fourth tested list	list 1–4
35	x̄	95.7	96.2	98.0	97.5	96.9
	SD	7.8	6.8	3.4	4.2	5.8
	SEM	1.7	1.5	0.8	0.9	0.6
20	x̄	91.0	93.1	95.6	92.9	93.2
	SD	10.9	10.7	6.6	9.9	9.6
	SEM	2.4	2.4	1.5	2.2	1.1
10	x̄	60.2	77.5	67.9	75.3	70.2
	SD	30.0	27.4	26.6	20.1	6.6
	SEM	6.7	6.1	5.9	4.5	3.0
0	x̄	17.5	15.4	17.5	20.2	17.7
	SD	22.9	16.9	21.5	20.4	20.2
	SEM	5.1	3.8	4.8	4.6	2.3

excepted. In very good or very difficult listening conditions, i e at the top or the bottom of the performance – intensity curve the differences in discrimination between the test subjects should always be small

However when the results were analysed with respect to the test sequence of the lists, i e the first, second, third and fourth list tested the score for the list tested first in frequency – distorted speech was reduced, compared with the other three lists in the test as seen in table IV No such differences were found between the lists in the other tests.

In order further to evaluate the disparity in performance between the different lists of frequency – distorted speech, the following calculations were made. The discrimination score at 35 dB sensation level for each of the four lists within the six different test was weighed by multiplying the scores by the factors –2 –1 +1 and +2 respectively and the values obtained by each test subject were summed. A sum around zero would then indicate that the performances with the four lists were fairly close to each other A positive value on the other hand suggested an effect of practice on the results

Analysed in this way the medians of the weighted sums for the test subjects were around zero in all tests, with the exception for frequency – distorted speech, where the median value was +44 4 This positive value thus shows that better scores were obtained for the lists tested last then for the list tested first. The corresponding median value for frequency – distorted speech, analysed

Table VII Mean discrimination scores and standard deviations obtained by 20 young subjects on distorted speech tests, presented at 35 dB sensation level

Test	List number		Number of sentences tested in each list: 7	13	25
Interrupted speech 10 int/sec	1	$\bar{x}$	98.7	99 3	99.5
		SD	2.1	1.2	0 8
		SEM	0 5	0 3	0.2
	2	–	96 8	97 6	98 6
		SD	4 5	3 2	1 8
		SEM	1 0	0 7	0 4
Interrupted speech 7 int./sec	1	–	97 1	98 2	98 4
		SD	5 0	2.7	2 1
		SEM	1 1	0 6	0 5
	2	–	98 0	98 4	97.5
		SD	3 6	4 9	2 7
		SEM	1 3	0 8	0 6
Interrupted speech 4 int./sec	1	$\bar{x}$	85 0	84 6	89 7
		SD	9 0	7 3	5 0
		SEM	2 0	1 6	1 1
	2	–	91 8	91 7	89 6
		SD	7 1	7 0	6 8
		SEM	1 6	1 6	1.5
Frequency-distorted speech	1	$\bar{x}$	93.2	95 4	96 1
		SD	7.3	5 1	3 7
		SEM	1 6	1.1	0 8
	2	$\bar{x}$	94 1	94 8	94 0
		SD	7 8	4 4	4 2
		SEM	1 7	1 0	0 9
Time-compressed speech II	1	–	99 1	97 3	96 9
		SD	2 3	3 0	1 9
		SEM	0 5	0 7	0 4
	2	$\bar{x}$	99 1	99.3	99.3
		SD	2 0	1.3	0 9
		SEM	0 4	0 3	0 2

according to the test number of the lists was +9 8 Wilcoxon s matched – pairs signed – ranks test was also applied to the weight sums for each test The null – hypothesis could only be rejected at statistically significant level ($p<0.01$) for frequency – distorted speech i e the test results of frequency – distorted speech were influenced by the effect of practice

In view of these findings the disposition of the test material for frequency – distorted speech was changed in such a way that the list tested first was always used as a practice list presented at 35 dB sensation level Lists 2–4 were pooled and divided into two lists of 25 sentences each (one sentence was removed from the tape) The total means of the discrimination scores in each test at different sensation levels and standard deviations were calculated for materials I and II and the results are

Table VIII. Mean discrimination scores and standard deviations obtained by 20 subjects, 50–60 years old, on distorted speech tests presented at 35 dB sensation level

Test	Test order of lists		Number of sentences tested in each list 7	13	25	last 12
Interrupted speech, 10 int sec	1	x̄	78 5	84 3	90 4	95 9
		SD	20 4	16 8	10 7	6 5
		SEM	4.6	3.8	2 4	1 5
	2	x̄	92.6	94 3	96.3	98 3
		SD	7 9	5 7	3.8	2 9
		SEM	1.8	1.3	0.8	0 6
Interrupted speech, 7 int/sec	1	x̄	83 3	89.6	91 9	94 5
		SD	12.8	8.1	5.2	4 6
		SEM	9	1 8	1.2	1 0
	2	x̄	89 6	92.8	94 0	95 4
		SD	9.5	6 0	4 7	4 8
		SEM	[illegible]1	1 4	1 1	1 1
Interrupted speech, 4 int/sec	1	x̄	58 9	60.3	63 9	68 9
		SD	0 7	16 6	14 0	17 6
		SEM	4.6	3.7	3 1	3 9
	2	x̄	61 2	62 2	63.5	63.2
		SD	22 4	16 1	16 1	21.3
		SEM	5 0	3 6	3.6	4 8
Frequency-distorted speech	1	x̄	79 4	84 4	86 3	87.9
		SD	18.2	14 1	11 4	11 6
		SEM	4 1	3 2	2 5	2 6
	2	x̄	79 2	85 9	88 9	91 4
		SD	14 3	9 5	8 4	9 4
		SEM	3 2	2 1	1 9	2.1
Time-compressed speech II	1	x̄	88 7	91 6	92 3	93 2
		SD	11 0	7 0	7 0	8 6
		SEM	2 5	1 6	1 6	1 9
	2	x̄	92 8	92 7	93 5	93 9
		SD	9 6	8 6	8 1	8 4
		SEM	2 1	1 9	1 8	1 9
Time-compressed speech I	1	x̄	93 2	95 0	96 3	98 0
		SD	10 0	7 0	4 7	3 1
		SEM	2 2	1 6	1 1	0 7
	2	x̄	95 2	95 4	97 2	99 2
		SD	7 1	5 6	3 5	2 1
		SEM	1 6	1 3	0 8	0 5

1 first tested list 2 = second tested list

Table IX. Mean discrimination scores and standard deviations obtained by 20 young and 20 "old" subjects on distorted speech tests, presented at 35 dB sensation level

Test	Test order of lists	young Mean	SD	SEM	"old" Mean	SD	SEM	difference
10 int/sec.	1	99.0	1.4	0.3	90.4	10.7	2.4	sign.
	2	99.1	1.6	0.3	96.3	3.8	0.8	
7 int/sec.	1	98.0	1.8	0.4	91.9	5.2	1.2	sign.
	2	97.5	3.0	0.7	94.0	4.7	1.1	sign.
4 int/sec.	1	88.8	6.2	1.4	63.9	14.0	3.1	sign.
	2	90.8	5.9	1.3	63.5	16.1	3.6	sign.
Frequency-distorted speech	1	95.4	3.6	0.8	86.3	11.4	2.5	
	2	94.8	4.5	1.0	88.9	8.4	1.9	
Time-compressed speech II	1	98.2	1.8	0.4	92.5	7.0	1.6	sign.
	2	97.9	2.1	0.5	93.5	8.1	1.8	

1 first tested list   2 second tested list

given in fig. 9. As can be seen, the performance – intensity curves for both materials largely coincide.

In materials III and IV consisting of 20 test subjects in each group the first two lists in each test were presented in randomized order at a sensation level of 35 dB.

The results were analysed with regard to the performance in discrimination of the first 7, 13 and the total number of 25 sentences in each list. In material IV the mean discrimination score was also calculated for the last 12 sentences in each list. The results are given in tables VII and VIII.

The differences in discrimination scores, when 7, 13 or 25 sentences were tested, were minimal in the group of young subjects, as were the standard deviations.

In the "old" group on the other hand the results were consistently lower for the first 7 sentences tested than for the last 1 sentences. This difference was most striking in the test with 10 int/sec.

It is also obvious that the capacity was lower throughout in the "old" group than in the young test group. A comparison of the test results calculated with regard to the test order of the lists, is given in table IX. The Wilcoxon's – Mann – Whitney rank order test was applied to the scores.

Statistically significant differences (p<0.01) were found between the two age groups in most of the tests. The exceptions were frequency – distorted speech, and the second list tested in time compressed speech and interrupted speech with 10 int/sec.

The results obtained in materials III and IV were also analysed for differences in performance between the right and left ear. Wilcoxon's matched – pairs signed – rank test was applied to the calculated difference for each participant. The null-hypothesis could not be rejected at a significance level of p<0.01, i.e., no demonstrable differences in performance was found between right and left ear in any test in the two age-groups.

Competing speech test

In this binaural test, the discrimination score was obtained by calculating the percentage of correct repeated SPB-words, heard in one ear simultaneously with sentences in the other ear. The mean discrimination score for 15 young test subjects was found to be 99.2% for the right ear and 98.4% for the left.

DISCUSSION OF RESULTS

The results on the different forms of distorted speech tests showed very high discrimination scores at a sensation level of 35 dB and the performance was fairly unaffected until the intensity of the speech was reduced to 10–15 dB sensation level.

A comparison between the results for materials II and III showed, that the scores were constantly higher in material III at 35 dB sensation level. An

according to the test number of the lists was +9 8 Wilcoxon s matched – pairs signed – ranks test was also applied to the weight sums for each test The null – hypothesis could only be rejected at *statistically significant level (p<0 01) for frequen* cy – distorted speech i e the test results of frequency – distorted speech were influenced by the effect of practice

In view of these findings the disposition of the test material for frequency – distorted speech was changed in such a way that the list tested first was always used as a practice list presented at 35 dB sensation level Lists 2–4 were pooled and divided into two lists of 25 sentences each (one sentence was removed from the tape) The total means of the discrimination scores in each test at different sensation levels and standard deviations were calculated for materials I and II and the results are

Table VIII. Mean discrimination scores and standard deviations obtained by 20 subjects, 50–60 years old on distorted speech tests presented at 35 dB sensation level.

Test		Test order of lists	Number of sentences tested in each list 7	13	25	last 12
Interrupted speech, 10 int sec	1	x̄	78.5	84.3	90 4	95 9
		SD	20 4	16 8	10 7	6.5
		SEM	4 6	3 8	2.4	1.5
	2	x̄	92.6	94.3	96.3	98.3
		SD	7 9	5 7	3 8	2.9
		SEM	1 8	1.3	0 8	0 6
Interrupted speech, 7 int/sec	1	x̄	83.3	89.6	91 9	94.5
		SD	12.8	8.1	5.2	4.6
		SEM	2 9	1 8	1 2	1 0
	2	x̄	89 6	92.8	94 0	95 4
		SD	9.5	6 0	4 7	4.8
		SEM	2 1	1 4	1 1	1 1
Interrupted speech, 4 int/sec	1	x̄	58 9	60 3	63 9	68 9
		SD	20 7	16 6	14 0	17 6
		SEM	4 6	3 7	3 1	3 9
	2	x̄	61 2	62 2	63.5	63 2
		SD	22 4	16 1	16 1	21.3
		SEM	5 0	3 6	3 6	4.8
Frequency-distorted speech	1	x̄	79 4	84 4	86 3	87 9
		SD	18	14 1	11 4	11 6
		SEM	4 1	3 2	2 5	2 6
	2	x̄	79 2	85 9	88 9	91 4
		SD	14 3	9 5	8 4	9 4
		SEM	3 2	2 1	1 9	2.1
Time-compressed speech II	1	x̄	88 7	91 6	92 5	93 2
		SD	11 0	7 0	7 0	8 6
		SEM	2 5	1 6	1 6	1 9
	2	x̄	92 8	92 7	93 5	93 9
		SD	9 6	8 6	8 1	8 4
		SEM	2 1	1 9	1 8	1 9
Time-compressed speech I	1	x̄	93 2	95 0	96 3	98 0
		SD	10 0	7 0	4 7	3 1
		SEM	2 2	1 6	1 1	0 7
	2	x̄	95 2	95 4	97 2	99 2
		SD	7 1	5 6	3 5	2 1
		SEM	1 6	1 3	0 8	0 5

1 = first tested list 2 second tested list

the test subjects had had no practice before the test session.

Time – compressed speech

The effect on discrimination when the speech rate was increased from normally 130 wpm to around 220 and 290 wpm respectively was minimal. The scores for the young test subjects exceeded 95% for the fastest speech rate. Also in the group of old subjects the performance was as high as 93% in this test. The time – compression in this investigation was not so pronounced as in similar tests performed by Bocca and Calearo (1963) de Quiros (1964), and Teatini (1970a). They used a speech rate of 350 wpm, which naturally gave lower scores than those achieved in this study.

Comparison of number of sentences tested

Analyses of the results in material III showed that the differences in discrimination when 7, 13 or 25 sentences were tested were minimal in young test subjects. The significance of this finding was that the number of sentences tested in each test could be reduced, if desired, to 7 and still give reliable results. This is worth knowing when handling young patients with central hearing disorders. The patients often have to undergo several examinations, and it is desirable to reduce the testing time as far as possible without lowering the reliability of the results.

When the results for the "old" test group were analysed with regard to 7, 13 or 25 sentences tested, a minor but clear effect of practice was found in all tests (table VIII). This finding was most obvious in the test with 10 int/sec. In the other tests, this effect of practice was not so pronounced probably because the test with 10 int/sec was always the one presented first to the listeners.

These findings show that elderly patients must get accustomed to the distorted speech tests, and that 50 sentences, i.e. 2 lists are necessary for each test session if the results are to be reliable.

Comparison between right and left ear performance

The left hemisphere dominance in speech reception mechanism is well known. This holds not only for right handed subjects, but also for the majority of left-handed subjects, as shown by Penfield and Roberts (1959).

It was therefore considered worth while to determine whether there is an asymmetry between the hemispheres in recognition of distorted speech tests. Earlier investigations by Calearo and Antonelli (1963) and Dirks (1964) could not prove any differences between right and left ear performance under monaural listening conditions. The results in this study are in agreement with these findings, both for the young and old group. On the other hand, Broadbent (1954), Kimura (1961 a,b), Dirk (1964), Milner (1965), Katz (1962, 1968) and others found that significantly more words were recognized by the right ear contralateral to the dominant hemisphere under dichotic listening conditions. This implies that during competition between the auditory pathways there is an asymmetry between the sides. They also found that when the test subject had to concentrate on one ear and ignore the message simultaneously given to the other ear there were no significant differences between the sides. In this study of the performance on competing speech this observation was confirmed, as the discrimination score was the same for both the right ear and the left.

ADJUSTMENT OF THE TEST BATTERY FOR CLINICAL USE

The test battery with 7 *different* forms of distorted speech tests, is fairly extensive and might be difficult to manipulate in *routine* work. As a rule the patients have to undergo not only these special tests, but also several of time-consuming and tiring audiological and vestibular examinations. It is thus desirable to reduce the testing time if possible and this can be done by selectively reducing the number of distorted speech tests used.

Periodically interrupted speech was constructed in three different forms with 10, 7 and 4 int/sec respectively. The test with 10 int/sec. was rather easy to perform because of the short off time (50 msec) of the speech signals. On the other hand the test with 4 int/sec. was fairly difficult owing to the long off time of 125 msec. The test with 7 int/sec was of average difficulty and is the best test to start with. If for some reason, this test with 7 int/sec did not give the diagnostic information,

explanation for this difference can be offered only concerning frequency – distorted speech i e the test subjects in material III were used to listening to the distorted speech before the test session had been started As for the other tests the differences in performance might be explained by the assumption that it is easier to listen to a speech test that is constant in intensity than to a test where the sound pressure levels are continously varied

Antonelli (1970a) the performance in this group of elderly subjects was as a whole much better in all tests. In test subjects, 50–70 years old Kirikae found a mean discrimination score of 30% at 5 int/sec. Similar results were also obtained by Antonelli with the most difficult forms of periodical interrupted speech, while the easier test with 10 int/sec gave values close to those in this study

Interrupted speech

The effect on discrimination when the speech information is reduced by periodical interruption is not very pronounced in young test subjects. In the tests with 10 and 7 int/sec respectively the scores exceeded 95% at 35 dB sensation level Also for the test with 4 int/sec where the off time was 125 msec and thus a fair amount of information was cancelled, the scores were still above 80% These findings are in fairly good agreement with those of Miller and Licklider (1950) Calearo and Antonelli (1963) Korsan Bengtsen (1968) and Teatini (1970a) at least for the higher degrees of interruptions. Minor differences in discrimination scores can undoubtedly be ascribed to differences in the speech material used It is noteworthy that no effect of practice was observed in these young test subjects (see table VII) This is not in agreement with the results of Miller and Licklider who found that practice increased the score by 25–30% compared with listeners without such practice

On the other hand this training effect of practice was observed very clearly in the old group as shown in table VIII The score for the test presented first 10 int/sec was increased by almost 20% from the first 7 sentences tested compared with the last 12 sentences in the second list Similar tendencies, though not so pronounced were also observed for the test with 7 int/sec But a more interesting finding was that the most difficult test the test with 4 int/sec., showed the slightest effect of practice The explanation might be that the test is so difficult that more than two lists are necessary to overcome the difficulties. This extension of the test was however not performed The standard deviations were also very large in this test in the old group owing to wide variations in performance between the test subject.

Compared with the results of Kirikae (1964) and

Frequency – distorted speech

Analyses of the results in material II with a randomized order between the test lists clearly showed that the performance on frequency – distorted speech was influenced by practice The other tests did not show this effect The score at a sensation level of 35 dB when practice preceeded the test session was around 95% for the young test group while the mean score without practice was 84% as seen in materials I and II This training effect has not been taken into account in earlier studies

The effect on the discrimination of frequency – distortion in young normals has been widely investigated by among others Bocca Calearo and Migliavacca (1955) Lindén (1960) Bocca and Calearo (1963) Kirikae (1964) and Teati[illegible] (1970a).

The results varied depending on the type [illegible] filters used i.e low pass-or band pass filters, a[illegible] also the type of speech material presente[illegible] Usually the scores obtained were around 60–8[illegible] at a sensation level of 35 dB and thus much low[illegible] than in the present investigation

In spite of practice in the group of elderly te[illegible] subjects the scores were lower than in the you[illegible] test subjects. The mean scores (table VIII) we[illegible] slightly below 90% There was also a minor effe[illegible] of practice that persisted throughout the tests [illegible] the performance on the first tested 7 sentenc[illegible] was lower than on the last 12 sentences tested

The scores in this study were much higher tha[illegible] those reported by Antonelli (1970a) who teste[illegible] elderly patients with normal hearing He use[illegible] frequency – bands, which gave roughly the effec[illegible] of a 500 Hz low pass filter With sentences as tes[illegible] material the score was only 25% at 35 d[illegible] sensation level The differences might be due t[illegible] both different filters and higher age in his tes[illegible] group but also to the reduced performance when

V Clinical part

Evaluation of distorted speech tests in patients with peripheral hearing loss

In some patients with central hearing disorders also peripheral hearing may be impaired. It was therefore decided to check the performance of distorted speech tests in patients with hearing loss due to changes in the middle ear or the cochlea.

Earlier reports on the influence of peripheral hearing disorders on the discrimination of distorted speech tests are not very comprehensive. Katz (1962, 1963), de Quiros (1964) and Korsan-Bengtsen (1970a) thus found that pure conductive hearing loss did not alter the performance of distorted speech tests. In cochlear lesions, on the other hand, they found the scores achieved in these special tests to be abnormally low. Similar effects with the use of time-compressed speech on young patients with sensorineural hearing loss have also been reported by Schon (1970). Using synthetic sentences as test material Jerger (1970b) did not find cochlear disorders to affect the performance of competing and interrupted speech tests. In order further to analyse the effect of peripheral hearing loss on the discrimination of distorted speech tests, the following investigation was carried out.

I. Two lists in each test were presented at a sensation level of 35 dB to 11 patients, all together 14 ears, with a pure conductive hearing loss. Their mean age was 79 years. The cause of the middle ear damage was otosclerosis or chronic otitis. The average tone hearing threshold on the impaired side was 40.9 dB and the mean discrimination score 98.3%.

II. Two lists in each test were presented to 8 patients, all together 15 ears, with congenital sensorineural hearing loss of moderate severity. Their mean age was 25 years. The mean *pure tone* threshold was 33.0 dB and the mean discrimination score 97.9%. In order to find out whether a cochlear lesion was the cause of the impaired hearing the stapedial reflex threshold was recorded in all ears. The recording technique used was that of Klockhoff (1961), Lidén et al (1970, 1972). The stimuli consisted of tones within the frequency range 250–4000 Hz. A normal reflex threshold was recorded in all ears indicating a cochlear lesion. The cause of the impaired hearing was heredity or birth trauma. All patients had been regularly controlled for many years, and repeated hearing tests did not reveal any progress of the hearing impairment.

III. Two lists in each test were presented to 10 patients, all together 10 ears, with acquired sensorineural hearing loss. The test group was made up of patients with losses due to Ménière's disease, trauma or cochlear otosclerosis. In no case had the hearing impairment existed more than 5 years. The mean age of the patients was 38 *years. The* average hearing loss for pure tones was 34.6 dB and the mean discrimination score was 93.2%. Measurement of the stapedial reflex threshold revealed a cochlear lesion in all the cases.

RESULTS

The *results* of distorted speech tests in the three groups with peripheral hearing loss are given in table X. *As* can be seen the patients with conductive hearing loss manage the special tests almost as good as normal hearing test subjects.

In the two groups with sensorineural loss caused by cochlear lesions, there was a discrepancy between the congenital and acquired" group. The scores for the former group, i.e. with congenital hearing loss, were surprisingly high, and in the easiest tests approached the results obtained in the normals. In the group with acquired *hearing loss* on the other hand, the scores were markedly reduced in all tests, in spite of almost identical hearing loss on the tone *audiogram* as those with congenital cochlear impairment. Test results in two cases, one with acquired and one with a congenital lesion, are shown in figures 10 and 11.

i.e. was too easy or too difficult for the patient the test session could be continued with one of the other forms of interrupted speech tests.

The same argument holds also for time compressed speech where it was suitable to start with the highest speech rate i.e. 290 wpm. When this speed was too difficult for the patient the *lower speech rate of 220 wpm was used*

It is clear from table VII that in young test subjects it was sufficient to test only one list in each test half of it presented to one ear the other half to the other But in elderly test subjects the results showed that it was advisable to test a whole list on each ear if the results were to be reliable

The test were usually presented at a sensation level of 35 dB As the performance – intensity curves were very steep (fig 9) a lower intensity was used when desired Judging from experience with this test battery the best choice of primary tests are those with interrupted speech with 7 *int/sec frequency – distorted speech preceded* by practice time – compressed speech II and competing speech test Using one list in each test it will take about 20–30 minutes to go through a test battery of this design.

V Clinical part

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I. Two lists in each test were presented at a sensation level of 35 dB to 11 patients, all together 14 ears with pure conductive hearing loss. Their mean age was 29 years. The cause of the middle ear damage was otosclerosis or chronic otitis. The average tone hearing threshold on the impaired side was 40.9 dB and the mean discrimination score 98.3%.

II. Two lists in each test were presented to 8 patients, all together 15 ears with congenital sensorineural hearing loss of moderate severity. Their mean age was 25 years. The mean pure tone threshold was 33.0 dB, and the mean discrimination score 97.9%. In order to find out whether a cochlear lesion was the cause of the impaired hearing the stapedial reflex threshold was recorded in all ears. The recording technique used was that of Klockhoff (1961), Lidén et al (1970, 1972). The stimuli consisted of tones within the frequency range 250–4000 Hz. A normal reflex threshold was recorded in all ears, indicating a cochlear lesion. The cause of the impaired hearing was heredity or birth trauma. All patients had been regularly controlled for many years, and repeated hearing tests did not reveal any progress of the hearing impairment.

III. Two lists in each test were presented to 10 patients, all together 10 ears with acquired sensorineural hearing loss. The test group was made up of patients with losses due to Ménière's disease, trauma or cochlear otosclerosis. In no case had the hearing impairment existed more than 5 years. The mean age of the patients was 38 years. The average hearing loss for pure tones was 34.6 dB and the mean discrimination score was 93.2%. Measurement of the stapedial reflex threshold revealed a cochlear lesion in all the cases.

RESULTS

The results of distorted speech tests in the three groups with peripheral hearing loss are given in table X. As can be seen the patients with conductive hearing loss manage the special tests almost as good as normal hearing test subjects.

In the two groups with sensorineural loss, caused by cochlear lesions, there was a discrepancy between the "congenital" and "acquired" group. The scores for the former group, i.e. with congenital hearing loss, were surprisingly high, and in the easiest tests approached the results obtained in the normals. In the group with acquired hearing loss on the other hand the scores were markedly reduced in all tests, in spite of almost identical hearing loss on the tone audiogram as those with congenital cochlear impairment. Test results in two cases, one with acquired and one with a congenital lesion, are shown in figures 10 and 11.

i e was too easy or too difficult for the patient the test session could be continued with one of the other forms of interrupted speech tests.

The same argument holds also for time compressed speech where it was suitable to start with the highest speech rate i e 290 wpm. When this speed was too difficult for the patient the lower speech rate of 220 wpm was used

It is clear from table VII that in young test subjects it was sufficient to test only one list in each test half of it presented to one ear the other half to the other But in elderly test subjects the results showed that it was advisable to test a whole list on each ear if the results were to be reliable

The test were usually presented at a sensation level of 35 dB As the performance – intensity curves were very steep (fig 9) a lower intensity was used when desired Judging from experience with this test battery the best choice of primary tests are those with interrupted speech with 7 int/sec., frequency – distorted speech preceded by practice time – compressed speech II and competing speech test Using one list in each test it will take about 20–30 minutes to go through a test battery of this design.

V Clinical part

Evaluation of distorted speech tests in patients with peripheral hearing loss

In some patients with central hearing disorders also peripheral hearing may be impaired It was therefore decided to check the performance of distorted speech tests in patients with hearing loss due to changes in the middle ear or the cochlea

Earlier reports on the influence of peripheral hearing disorders on the discrimination of distorted speech tests are not very comprehensive Katz (1962 1963), de Quiros (1964) and Korsan-Bengtsen (1970a) thus found that pure conductive hearing loss did not alter the performance of distorted speech tests In cochlear lesions, on the other hand they found the scores achieved in these special tests to be abnormally low Similar effects with the use of time – compressed speech on young patients with sensorineural hearing loss have also been reported by Schon (1970) Using synthetic sentences as test material Jerger (1970b) did not find cochlear disorders to affect the performance of competing and interrupted speech tests In order further to analyse the effect of peripheral hearing loss on the discrimination of distorted speech tests the following investigation was carried out

I Two lists in each test were presented at a sensation level of 35 dB to 11 patients, all together 14 ears with a pure conductive hearing loss Their mean age was 29 years The cause of the middle ear damage was otosclerosis or chronic otitis The average tone hearing threshold on the impaired side was 40 9 dB and the mean discrimination score 98 3%

II Two lists in each test were presented to 8 patients, all together 15 ears, with congenital sensorineural hearing loss of moderate severity Their mean age was 25 years The mean pure tone threshold was 33 0 dB and the mean discrimination score 97 9% In order to find out whether a cochlear lesion was the cause of the impaired hearing the stapedial reflex threshold was recorded in all ears The recording technique used was that of Klockhoff (1961) Lidén et al (1970 1972). The stimuli consisted of tones within the frequency range 250–4000 Hz A normal reflex threshold was recorded in all ears, indicating a cochlear lesion. The cause of the impaired hearing was heredity or birth trauma. All patients had been regularly controlled for many years, and repeated hearing tests did not reveal any progress of the hearing impairment.

III Two lists in each test were presented to 10 patients all together 10 ears, with acquired sensorineural hearing loss. The test group was made up of patients with losses due to Ménière's disease trauma or cochlear otosclerosis. In no case had the hearing impairment existed more than 5 years. The mean age of the patients was 38 years. The average hearing loss for pure tones was 34.6 dB and the mean discrimination score was 93.2% Measurement of the stapedial reflex threshold revealed a cochlear lesion in all the cases.

RESULTS

The results of distorted speech tests in the three groups with peripheral hearing loss are given in table X. As can be seen the patients with conductive hearing loss manage the special tests almost as good as normal hearing test subjects.

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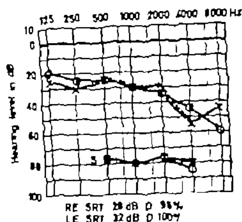
i.e was too easy or too difficult for the patient the test session could be continued with one of the other forms of interrupted speech tests.

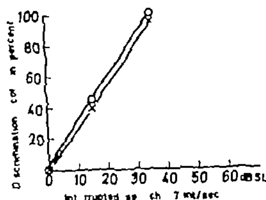
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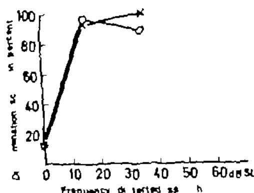
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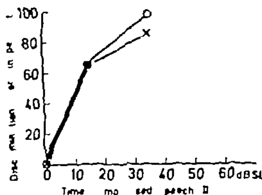


Fig. 11. Test results with ordinary and distorted speech tests in a patient with congenital sensorineural hearing loss.

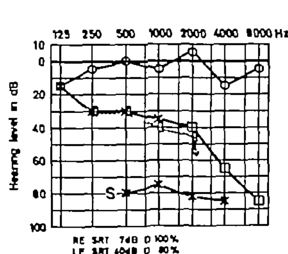
DISCUSSION OF RESULTS

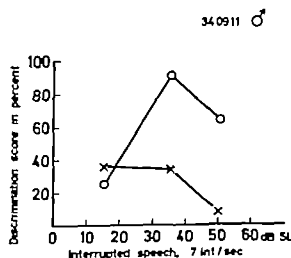
The performance in the group with conductive hearing loss was that expected. As long as the sound pressure level is raised enough to compensate for the attenuation in the middle ear these patients will manage the distorted speech tests equally well as normals. The performance intensity curves are displaced but retain the same shape as in normals.

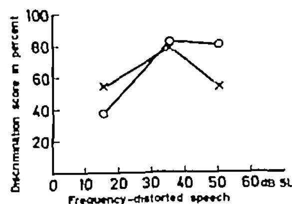
The difference in performance between the two groups with cochlear lesions is interesting. The reason why the results in patients with congenital sensorineural hearing loss were so good might be as follows. In these test subjects the central auditory system had been used for analysing speech signals somewhat reduced in redundancy by the cochlear lesion. When the speech signals were made still more low-redundant by means of different forms of distortions, the analytic function of CNS was not stressed more than in normals. In patients with acquired cochlear lesions, on the other hand the primordial processing of the speech signals is disturbed by the cochlear distortion. When the analytic and interpreting function of the central hearing mechanism is strained still more by addition of distorted speech signals to the ear the discrimination will be notably impaired.

Table X. Mean discrimination scores and standard deviations for distorted and undistorted speech audiometry in young patients with peripheral hearing loss.

Test	Conductive hearing loss (14 ears)	Sensorineural hearing loss congenital (15 ears)	Sensorineural hearing loss acquired (10 ears)
10 int/sec.	96 9±4.6	93 4±7.2	61.2±21 4
7 int/sec	95.8±2 3	89.5±10.9	60 1±20.2
frequency-distorted speech	87 6±15 8	95 9±5 0	46.5±25 8
time-compressed speech II	88 6±12.8	84.3±16.6	51 1±23 0
speech discrimination	98 3±2 6	97 9±4.2	93.2±6 6







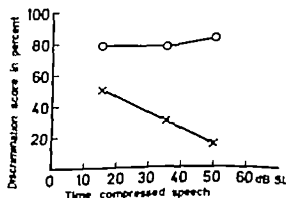
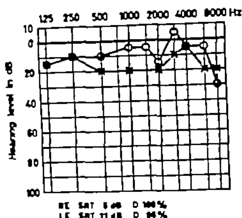
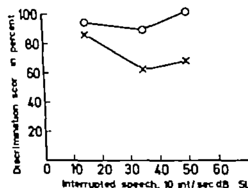


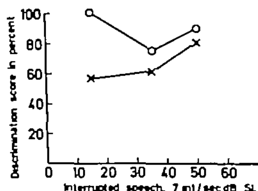
Fig 10 Test results with ordinary and distorted speech test in patient with sensorineural hearing loss, due to trauma, in the left ear

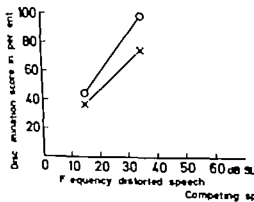
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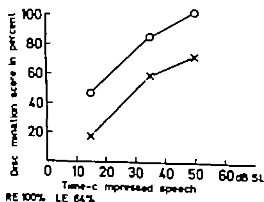












Competing speech RE 100% LE 64%

Fig. 12. Test results obtained with ordinary and distorted speech audiometry in patient with right-sided astrocytoma in the temporal lobe. The tests were performed 9 days after operation.
Dotted area denotes removed tumour

Evaluation of distorted speech tests in patients with intra-cranial lesions

As mentioned in part III it is possible to detect disturbances in the central hearing mechanism by speech tests which are made low-redundant by various forms of distorsions In order further to evaluate and classify auditory manifestations accompanying pathological changes in the central nervous system a group of patients with known intra-cranial lesions were tested

MATERIAL

Thirty-three patients aged 10–63 years with intra-cranial lesions were tested In twenty-six the lesion was situated in the temporal lobe either on the right side or on left Of these twenty-three had brain tumours two had intra-cerebral hematomas – one due to trauma one following a ruptured aneurysm Another temporal lesion was epileptogenic. Three patients had tumours in other parts of the hemispheres and four patients had brain stem tumours

All the patients except two had undergone a neurosurgical operation The two patients not explored had a tumour extending from the medulla up to the fourth ventricle in the pons

In order to determine the effect of lesions in various sites on the performance by the patients when tested with distorted speech material the thirty-three patients were classified according to the extent and location of their lesions. This classification was done jointly by a neurosurgeon and a neuroradiologist They judged the anatomical extent of the lesions from the X ray findings, surgeon s reports, gamma-encephalography EEG visual field defects and other clinical symtoms As a result of their assessments, the patients were divided into four different groups

I – Patients with temporal lobe lesions involving the auditory cortex

Eleven patients five women and six men had a unilateral temporal lobe lesion involving the auditory cortex The patients ages ranged from 14 to 63 years (mean 46) In ten cases the lesion was situated in the right temporal lobe In one patient the lesion was left-sided and though it was large he showed no signs of aphasia. Three patients were tested a few days before operation the other cases, 7 days *to 6 months after the operation* Only one case was tested 1 1/2 years after operation and then X-ray examination revealed a *recurrent tumour Representative cases are illustrated* in figs. 12–16 (the other 6 cases are illustrated in the appendix figs. 31–36)

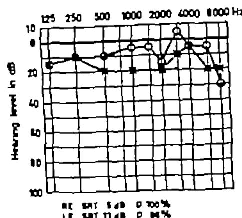
II a – Patients with temporal lobe lesions not involving the auditory cortex

Nine patients five women and four men had *unilateral temporal lobe lesions located in the temporal pole distant from the auditory cortex* The patients were 18 to 63 years old (mean 40 years) The lesion was right-sided in five and *left-sided in the remaining four None of the* patients had any sign of aphasia Three patients were tested only a few days before the operation *while six were tested post-operatively One* patient with an intra-cerebral hematoma was tested 5 days after the operation and one with a *meningioma 3 months post-operatively* The remaining four patients were tested 6 months – 1 year after the operation One of these patients was *operated upon because of epilepsy the others,* because of tumours In none of these patients did X-ray examination or clinical investigation reveal recurrence of the tumour Some cases are illustrated in figs 17–19

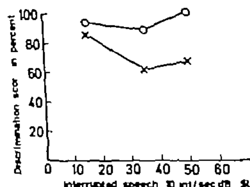
II b – Patients with temporal lobe lesions close to the auditory cortex

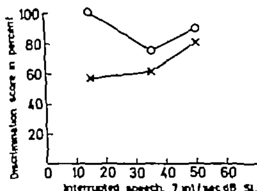
This group consisted of six patients four women and five men Their ages ranged from 34 to 53 years (mean 4) According to the neurosurgeon and the radiologist the temporal lobe lesions in this group *were situated very close to the auditory* cortex In some cases it was doubtful whether the

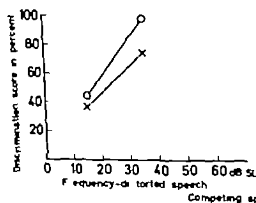
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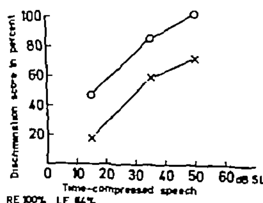












Competing speech RE 100% LE 64%

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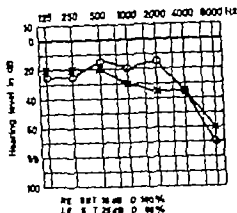
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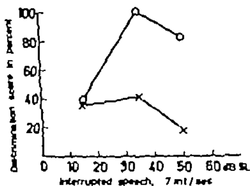
II b – Patients with temporal lobe lesions close to the auditory cortex

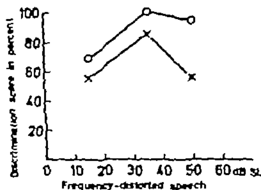
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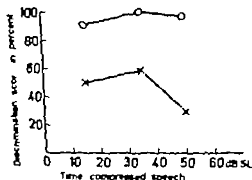
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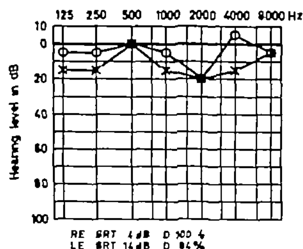




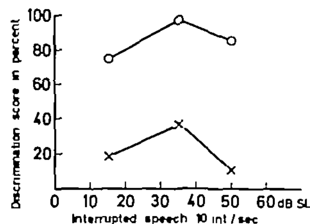


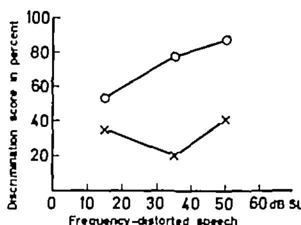
Competing speech RE 100% LE 68%

Fig. 14. Test results obtained with ordinary and distorted speech audiometry in a patient with glioblastoma in the right temporal lobe. The test were performed 10 days after operation.
Broken lines denote extent of the tumour.
Dotted area denotes removed tumour.









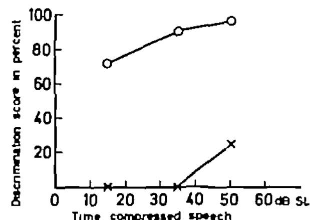
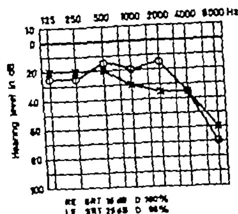
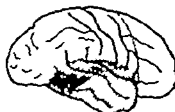
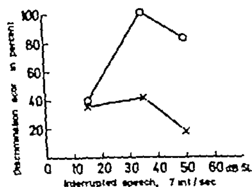


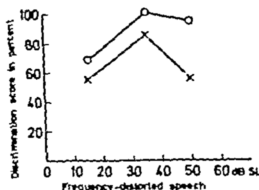
Fig 13 Test results obtained with ordinary and distorted speech audiometry in patient with local hematoma in the right temporal lobe due to a ruptured aneurysm The tests were performed 14 days afte operation
Dotted area denotes extent f the hematoma

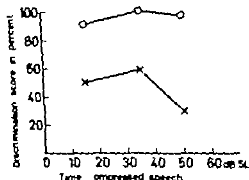
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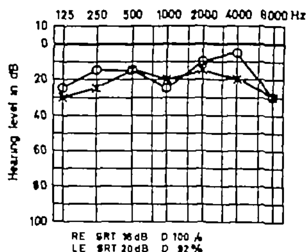


Competing speech RE 100 %

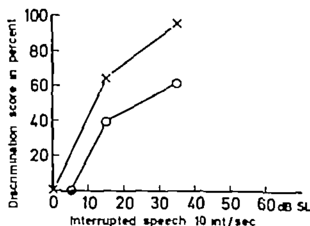
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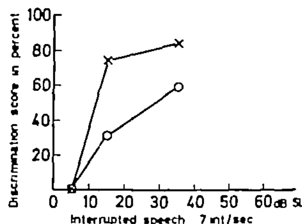
Broken lines denote extent of the tumour.

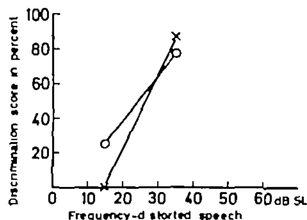
Dotted area denotes removed tumour.











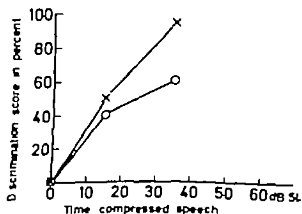
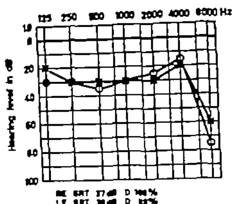


Fig. 15. Test results obtained with ordinary and distorted speech audiometry in a patient with an astrocytoma in the left temporal lobe. The tests were performed *1 1/2 years after operation.*
Broken lines denote extent of the tumour.
Dotted area denotes earlier resection of tumour.



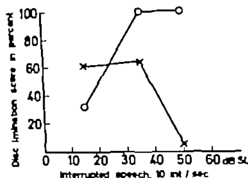
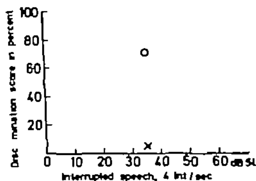
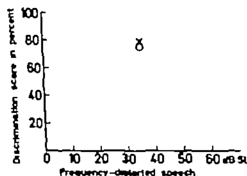
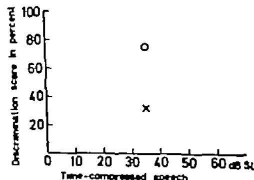
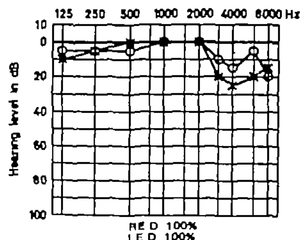
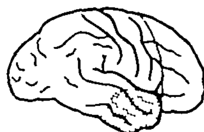
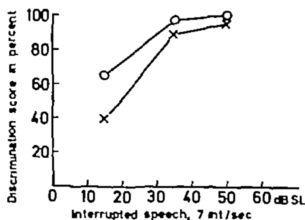





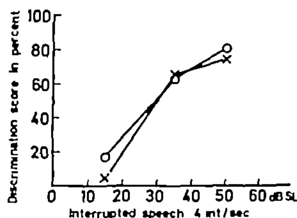
Fig. 16. Test results obtained with ordinary and distorted speech audiometry in a patient with glioblastoma in the right temporal lobe. The tests were performed 2 days before operation.
Dotted area denotes extent of the tumour.

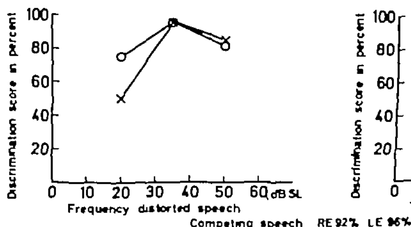
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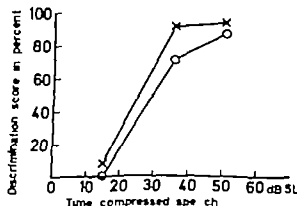
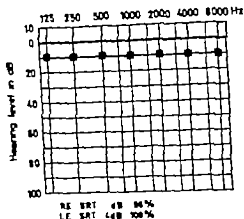


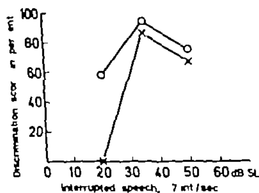
Fig. 17. Test result btained w th ordinary and dist rted speech audiometry in patient with an astrocytoma in the right temporal lobe. *The test were performed* 1 year after operation. X-ray examinations did not reveal any recurrence f the tumour.

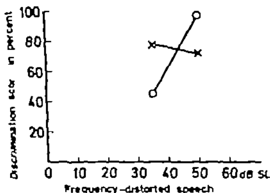
Dotted area denotes removed tumo r

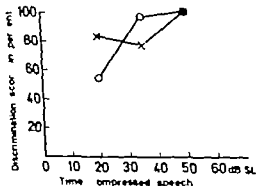
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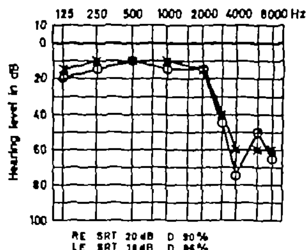






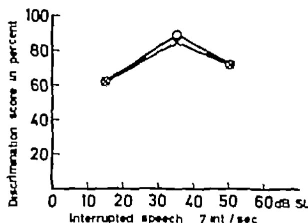
Competing speech RE 96%
LE 96%

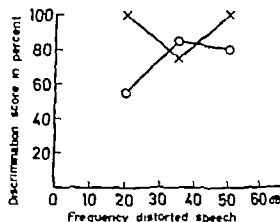
Fig. 18. Test results obtained with ordinary and distorted speech audiometry in patient operated upon because of bleeding in the right temporal lobe after trauma. The tests were performed 5 days after operation.
Dotted area denotes resected part of the temporal lobe.



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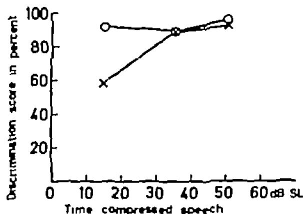


Fig. 19. Test results obtained with ordinary and distorted speech audiometry in a patient with a glioblastoma in the left temporal lobe. The tests were performed 6 months after operation.
Dotted area denotes removed tumour.

tumour had involved deeper structures underneath the cortex, or whether the tumour had displaced the whole temporal lobe and interfered with the function of the auditory cortex. Three of these patients were tested before the operation the other three post-operatively Two of these post operatively tested patients were examined respectively 1 and 2 years after the operation The tests were performed in connection with X-ray examination which had excluded recurrence of the tumour Two representative cases are shown in figs 20–21

III – Patients with intra-cranial tumours in other parts of the hemispheres

This group consisted of only three patients, all with expanding growing tumours One had a frontal lobe tumour on the left side the two a glioma in the parietal lobe one in the right lobe and the other in the left lobe In none of the cases did the tumour involve the auditory cortex or the hearing pathways The patients were tested 10 days 3 months after operation The scores achieved by the patient with a frontal lobe tumour are given in fig 22

IV – Patients with brain stem lesions

This group was made up of four patients Three of them were young, born in 1954–1962 and one a man in 1931 All of them showed multiple neurological signs owing to the infiltrative growth in the pons and adjacent structures Two patients were operated upon one patient received X-ray treatment and the fourth was not explored The diagnosis was made from neurological and X-ray findings The test results of one patient with a brain stem tumour are shown in fig 23

TEST METHODS

The patients with known intra-cranial lesions situated mainly in the temporal lobe were tested during a period of 2 1/2 years During this time the test methods were slightly modified In the earlier test sequences the performance – intensity curves were determined for each test and ear The presentation levels were 0,15 and 35 dB SL, or in most of the cases 15 or 20 35 and 50 dB SL, respectively The ipsilateral ear was always tested first

Later when distorted speech tests were included in the ordinary test battery two lists in each test were presented at 35 dB SL. The test battery was also condensed to comprise the following tests 7 interruptions/sec., frequency – distorted speech, preceded by practice time – compressed speech II and the competing speech test The test with 4 int/sec. was usually too difficult for the patient while the test with 10 int/sec. was often used besides the test with 7 int/sec Ordinary tone and speech audiograms were made on both ears before these special tests were carried out Examination of patients with brain stem lesions included supplementary tests including directional hearing test according to Nordlund (1963), tone decay test stapedial reflex threshold determinations and alternate binaural loudness balance test.

EQUIPMENT

The equipment used for testing these patients with intra-cranial injuries was the same as that described in part IV

In order to enlarge the series of patients with verified temporal lobe lesions, nine additional patients from the Neurosurgical Department Karolinska Hospital, Stockholm and Akademiska Hospital Uppsala, were admitted for tests. The author tested the patients at the Audiological Departments of the respective hospitals

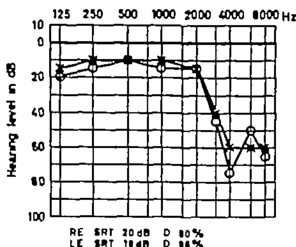
The equipment used in Stockholm was a dual channel Revox A 77 tape recorder which fed a Tegnér SA 4 speech audiometer Earphones THD 39 Mx 41 AR were used. Tegnér T 2 tone audiometer was used for determining the tone thresholds

In Uppsala the same tape recorder was used with a Madsen OB-70 tone and speech audiometer The earphones were THD 49 Mx 41 AR All tests were performed in sound proof rooms.

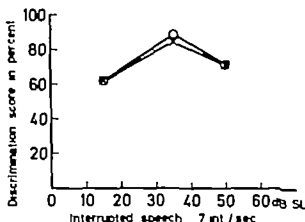
RESULTS

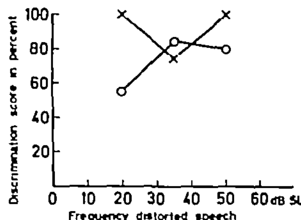
I – Patients with temporal lobe lesions involving the auditory cortex

The mean values of conventional audiograms were calculated for the eleven cases with unilateral temporal lobe lesions involving auditory cortex. As can be seen from fig. 24 the mean values for the contralateral ears were rather close to the









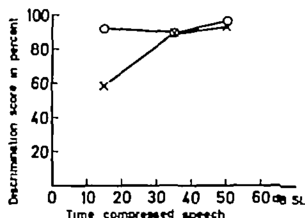
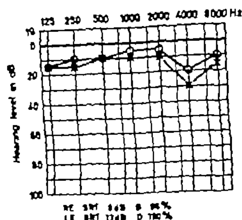
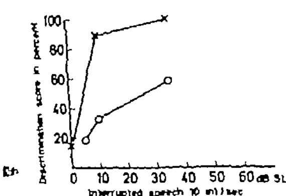


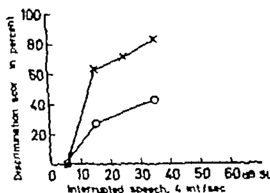
Fig. 19. Test results obtained with ordinary and distorted speech audiometry in a patient with a glioblastoma in the left temporal lobe. The tests were performed 6 months after operation.
Dotted area denotes removed tumour.

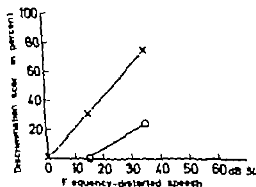
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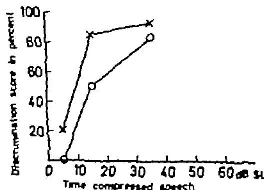
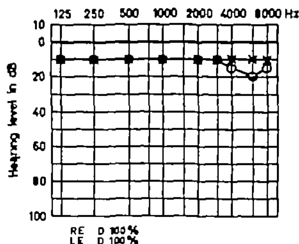
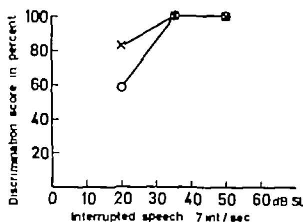
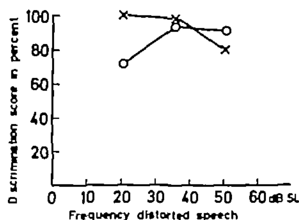


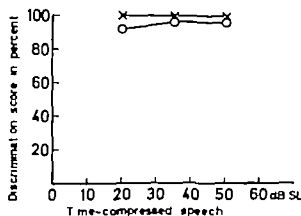
Fig. 21. Test results obtained with ordinary and distorted speech audiometry in a patient with an astrocytoma in the left temporal lobe. The tests were performed 11 days before operation.
Broken lines denote extent of the tumour.
Dotted area denotes removed tumour.







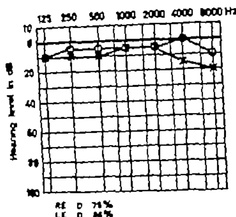


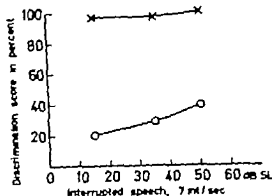


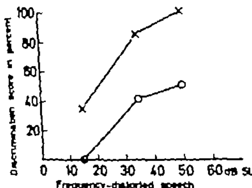
Competing speech RE 96 % LE 98 %

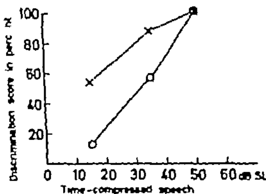
Fig 20 Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe The tests were performed 5 days before operation
Dotted area denotes extent of the tumour

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Competing speech RE 83% LE 90%

Fig. 23. Test results obtained with ordinary and distorted speech audiometry in patient with glioma of the brain stem.

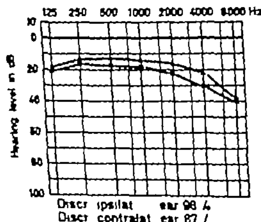


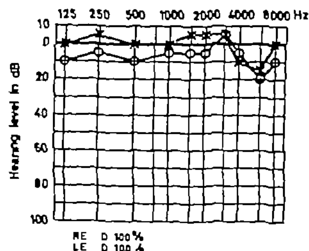
Fig. 24. Mean values of the tone- and speech audiograms for the ipsi- and contralateral ears in 11 patients with temporal lobe lesions, involving auditory cortex.

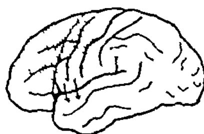
performance of those for the ipsilateral ears, whether it was the right or left ear that was tested. In the higher frequency range there was a minor difference between the ears. When ordinary speech, i.e. SPB-words, were used to determine the discrimination capacity, the mean difference between ipsi- and contralateral ears was 11%.

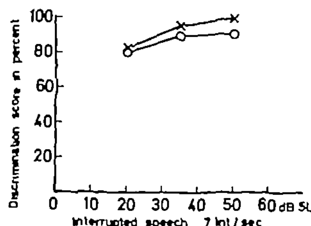
The mean scores achieved in the different forms of distorted speech tests are given in fig. 25.

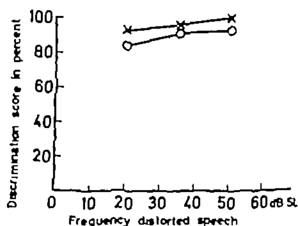
The test results clearly showed a large difference in performance between the ipsi- and contralateral ear in each test. This was most striking in the test with 10 int/sec, where the mean difference was nearly 65% at 50 dB sensation level. Also the test with the fastest form of time-compression, i.e. 290 wpm showed a mean difference of above 50% at 50 dB S.L. Frequency – distorted speech, on the other hand, showed the smallest difference

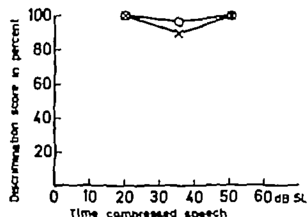
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Competing speech RE 100%
LE 92%

Fig. 22. Test results obtained with ordinary and distorted speech audiometry in patient with a glioblastoma in the left frontal lobe. The tests were performed 3 months afte operation.

Dotted area denotes removed tumour

Competing speech ipsilat ear 97%
contralat ear 94%

Fig. 27. Mean discrimination scores for the ipsi- and contralateral ears at five different forms of distorted speech audiometry in 9 patients with temporal lobe lesions situated distant from auditory cortex.

performance between the ipsi- and contralateral ears on the tone- and speech audiograms. The mean discrimination scores for different forms of distorted speech tests are given in fig. 27. Only very small differences in performance were found between ipsi- and contralateral ears in the test group. All patients were tested at 35 dB SL and at that level the mean scores were almost identical for both ears. Also no roll-over phenomenon was observed in this group compared with group I.

II b. – Patients with temporal lobe lesions, close to auditory cortex

Fig. 28 gives the mean values found at conventional audiometry in six patients with temporal lobe lesions close to the auditory cortex. Both ordinary tone- and speech audiograms

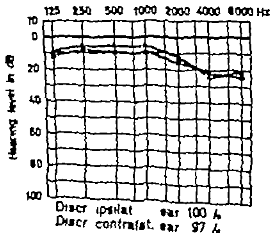


Fig. 28. Mean values of the tone- and speech audiograms in 6 patients with temporal lobe lesions, situated close to auditory cortex.

Comp t ng speech ps lat ear 95 %
cont alat 7§ %

Fig 25 Mean discrimination scores for the ipsi- and contralateral ears at five different forms of distorted speech audiometry in 11 patients with lesions in volving auditory cortex.

with only 32% at 50 dB S L between the ipsi and contralateral ear and at 35 dB S L the mean difference was 20%

The roll-over phenomenon which was found in all tests was interesting but most striking in the test with 10 int/sec and frequency – distorted speech *This roll-over effect has been described by* Jerger (1970a) and implies that the performance of the contralateral ear decreases at higher intensity *levels more than does that of normal ears*

II a – Patients with temporal lobe lesions not involving the auditory cortex

Fig 26 compares the mean values for conventional audiometry of the ipsi and contralateral ears in *nine patients with temporal lobe disorders It is* clearly seen that there was no difference in

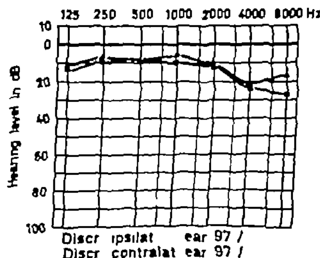


Fig 26 Mean ... lues of the tone and speech audiogram for the ipsi- and contralateral ears in 9 patient ... ith temporal lobe lesions, distant from aud tory ... x

Fig 27 Mean discrimination scores for the ipsi- and contralateral ears at five different forms of distorted speech audiometry in 9 patients with temporal lobe lesions situated distant from auditory cortex

performance between the ipsi- and contralateral ears on the tone- and speech audiograms. The mean discrimination scores for different forms of distorted speech tests are given in fig 27. Only very small differences in performance were found between ipsi- and contralateral ears in the test group. All patients were tested at 35 dB SL and at that level the mean scores were almost identical for both ears. Also no roll-over phenomenon was observed in this group compared with group I.

II b – Patients with temporal lobe lesions, close to auditory cortex

Fig 28 gives the mean values found at conventional audiometry in six patients with temporal lobe lesions close to the auditory cortex. Both ordinary tone and speech audiograms

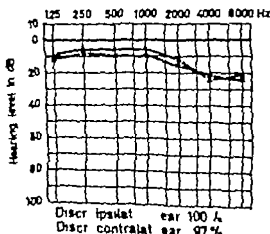
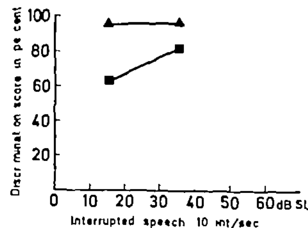
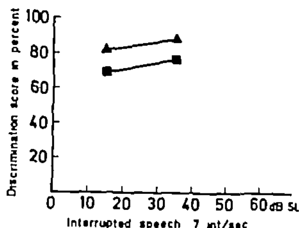
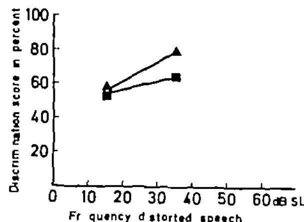
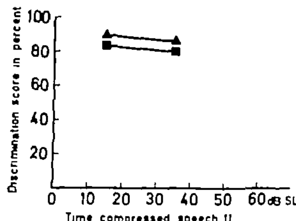


Fig 28 Mean values of the tone- and speech audiograms in 6 patients with temporal lobe lesions, situated close to auditory cortex









Competing speech ipsilat ear 96%
contralat ear 68%

Fig 29 Mean discrimination scores for the ipsi- and contralateral ears at five different forms of distorted speech audiometry in 6 patients with temporal lobe lesions situated close to auditory cortex

showed normal values with only minor differences between the ipsi and contralateral ears When tested with distorted speech a certain difference was found between the ipsi and the contralateral ears (fig 29) The differences were most pronounced for the interrupted speech tests while the mean scores achieved by the ipsi and contralateral ears for time – compressed speech with a speech rate of 290 wpm were fairly equal As none of the patients was tested at 50 dB SL, the roll-over phenomenon could not be evaluated

III – Patients with intra-cranial tumours in other parts of the hemispheres

Only three patients belonged to this group There fore no mean values were calculated either for

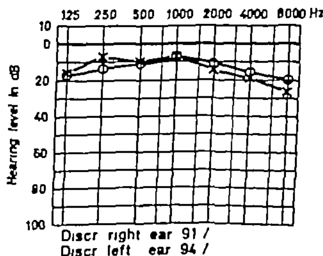


Fig 30 Mean tone- and speech audiogram in 4 patients with brain stem tumours

conventional or for distorted speech audiometry. As shown in fig. 22 the performance in the special hearing tests was quite normal. Similar normal audiological findings were also obtained in the other two cases.

IV – Patients with brain stem lesions

In the four patients with a brain stem lesion the latter was localized mainly to the right side of the brain stem. The mean tone and speech audiograms for the right and left ears were calculated and the results obtained were within normal values (see fig. 30). The results of distorted speech audiometry in a patient with a brain stem lesion are given in fig. 23. Corresponding results were also obtained in the three other patients. Supplementary audiological tests, comprising directional hearing test, determination of the stapedial reflex threshold and tone-decay test were also performed and clearly suggested a lesion of the brain stem.

DISCUSSION OF RESULTS

The mean hearing thresholds for pure tones (see figs. 24, 26, 28 and 30) showed only minor differences between the ipsi- and contralateral ears in the higher frequency range in group I. In groups II-IV the tone thresholds were largely equal for both ears. Noteworthy is the small difference in performance on undistorted speech audiometry between the ipsi- and contralateral ears in group I. In spite of fairly large destructive lesions involving the auditory cortex the mean discrimination score on the contralateral ear was only reduced by 11%. Five of the patients achieved normal scores, while the other six had discrimination scores ranging between 72% to 88%. In group II-IV the mean scores were almost identical for both ears. Thus ordinary tone and speech audiometry yields only little diagnostic information about lesions involving the auditory cortex and pathways. When monaural distorted speech tests were applied to patients with well defined temporal lobe lesions, a striking difference in performance was found between the ipsi- and contralateral ears in group I, i.e. with lesions involving the auditory cortex.

The most sensitive tests for revealing central hearing disturbances appeared to be (fig. 25) interrupted speech test with 10 interruptions/second and time-compressed speech with a speech rate around 790 wpm. In these tests, the mean difference in discrimination between the ipsi- and contralateral ears were above 50%. Frequency distorted speech showed the smallest difference viz. 32% at 50 dB sensation level.

In group II a with lesions distant from the auditory cortex, the mean scores coincided at 35 dB S.L. in all tests. As expected group II b with injuries close to the auditory cortex, showed minor differences between the ipsi- and contralateral ears. These results are not quite compatible with those obtained by Bocca (1963). He found that integration disturbances in the auditory cortex were best revealed by frequency – distorted speech, while tone – compressed and interrupted speech tests indicated lesions of the second neuron and diffuse central disorders.

The difference between Bocca's results and those obtained in this investigation might be explained by the differences in phonetic composition of the languages but also by the test methods. In this study the subjects practiced listening to frequency – distorted speech before the actual tests were started. With no practice and with the contralateral ear tested first the difference between the ipsi- and contralateral ear might be pronounced.

The results of competing speech tests in this study showed a mean difference in discrimination between the ears of 21% in group I. The performance on the ipsilateral ear was invariably normal while that on the contralateral ear ranged from 57% to 96%. In patients with lesions distant from the auditory cortex the mean difference was only 3%, while the corresponding figure for those with lesions close to auditory cortex was 12%. These differences are smaller than those found by Jerger (1964) in the same type of test but the achieved results in this study suggest that this binaural test is valuable for revealing central auditory disturbances.

In patients with lesions outside the temporal lobe, the results of tests with distorted speech in three patients studied were normal, i.e., no difference in performance between the ears. These results were expected as the results of tests with low-redundant speech were normal in group II a.

The validity of auditory tests for diagnosing brain stem lesions is not so well established as that of cortical auditory tests.

Brain stem involvement usually results in auditory dysfunctions such as more or less reduced

pure tone thresholds, decreased perception of undistorted speech positive tone decay test and recruitment phenomenon varying from absent to complete as reviewed by Eichel et al (1966) and Parker et al (1968) The directional hearing is abnormal (Nordlund 1963) Parker also found a typical tone perversion in cases with brain stem lesions. Test results with distorted speech have shown (Bocca 1958 Calearo and Antonelli 1963 1968 Antonelli 1970a Jerger 1964 1970c) that low scores were obtained in the ipsilateral ear in patients with nuclear lesions while involvement of the pathways after the crossing reduced the score of the contralateral ear The change in discrimination ability is often bilateral both for undistorted and distorted speech. This is due to the fact that the cochlear nuclei are located so close to each other in the floor of the fourth ventricle that a tumour in this region can very easily impair hearing on both sides In the four cases in this study the tumours were situated mainly to the right side of the brain stem and the scores for distorted speech were also much lower on the right side than on the left (see fig. 23) This indicates that the tumour had infiltrated mainly the right cochlear nuclei and had not grown rostrally in the region of the olivary complex Similar results were obtained in the three other patients with brain stem tumours.

The patients in group I had right sided lesions, except in one case thus a difference in performance between the right and left auditory cortex could not be evaluated However Calearo and Antonelli (1963) found no difference in performance between right and left sided lesions in distorted speech tests and there is no evidence arguing against this finding in monaural test situations

The roll-over phenomenon has been demonstrated by Bocca et al (1963) (cf figs 15 21 22) in brain stem and temporal lobe lesions, but the possible cause of this phenomenon has not been discussed It is noteworthy that the roll-over effect was also demonstrable on the ipsilateral side (cf fig 18) on presentation of frequency – distorted speech. Jerger (1970a) clearly demonstrated the phenomenon in patients with eighth nerve disorders as well as in 3 out of 6 patients with brain stem injuries

In the present study the roll-over effect was seen in group I in the test with 10 interruptions/second and frequency – distorted speech but only for the contralateral ear The performance on the ipsilateral side remained the same or increased slightly when the intensity of the speech signals was increased No explanation can be offered for the roll-over phenomenon In some but not all, patients with auditory cortical involvement the discomfort level of undistorted speech was determined and found to be normal for both ears

General discussion of audiological test results in patients with intra-cranial lesions

Audiological tests for evaluation of disturbances in the central hearing mechanism are restricted by the elusive diagnostic methods applied in these disorders In contrast with the peripheral auditory system, where signs of injuries can be revealed only the central auditory pathways and cortex may be seriously damaged with very little evidence of neurological deficits

As have been discussed in part III it is possible to evaluate changes in the central hearing mechanism by means of low-redundant speech tests (Bocca et al 1954 1963 Matzker 1959 Jerger 1960, 1964 Lindén 1960 Feldmann 1964 1967 Kimura 1961 Lynn 1972 and others)

The aim with the present study was to standardize different forms of distorted speech audiometry and to apply these tests, together with ordinary audiometry to patients with welldefined intra-cranial lesions The material consisted of thirty-three patients, twenty-six of whom had unilateral lesions in the *temporal lobe* either on the right side or the left The patients with temporal lobe lesions were classified according to the location and extent of the lesion into three groups e lesions involving the auditory cortex (I), lesions distant from the auditory cortex (II a) and those with lesions close to the auditory cortex (II b) The different tests with low-redundant speech audiometry included interrupted speech with 10 and 7 interruptions/sec time – compressed speech with speech rate of around 290 wpm frequency – distorted speech and competing test (see side 43)

The mean hearing thresholds for pure tones were calculated for the pre- and contralateral ears in each group It is noteworthy that even in group I there were only minor differences between the ears in the high frequency range The observed difference between the ears is probably an effect of the cortical and subcortical dysfunction as raised intra-cranial pressure should cause a symmetric decrease in pure tone hearing, especially in the high frequency range (von Wildhagen 1954 Jatho 1954 Hansen and Reske-Nielsen 1963). The differences obtained on the tone audiogram were however too small to permit a topical diagnosis The results in this study agree fairly well with those of other authors (Goldstein 1956 Bocca and Calearo 1963 Jerger 1960 et al, 1964 Kimura 1961 a, b) and are also supported by experimental studies on animals (Butler et al 1951 1957 Neff 1958 Tunturi 1960, Meuer et al 1952) The animal studies showed that bilateral ablation of auditory areas can be done without any consequent change in the discrimination of frequency and intensity of pure tones

The concept of cortical deafness in bilateral lesions in man reflected in decreased pure tone hearing has been the subject of some controversy Hearing loss, thought to be due to lesions in both *posterior* temporal lobes has been reported in early studies (Siebenmann 1896 Mott 1907 Henschen *1917 Bramwell 1927* and others) These reports however have not been universally accepted as representative of cortical deafness, as no analyses were made of premorbid auditory function, the degree of presbyacusis, earlier head trauma, presence of other systemic diseases etc. Thus DiCarlo et al (1962) denies the existence of even "a single convincing case study in which there is an unequivocally measured reduction in (auditory) sensitivity with a clearly demonstrable CNS lesion and no demonstrable peripheral lesion"

Jerger et al (1969), however demonstrated advanced bilateral hearing loss in a patient who sustained two separate cerebral hemisphere infarctions with maximal damage in both temporal lobes. Both tone and ordinary speech *tests* showed a pronounced hearing loss initially but with fairly quick recovery to almost normal hearing

The intelligibility of undistorted speech audiometry showed only a small difference in discrimination between the ipsi- and contralateral ears in the patients with lesions involving the auditory

pure tone thresholds, decreased perception of undistorted speech positive tone decay test and recruitment phenomenon varying from absent to complete as reviewed by Eichel et al (1966) and Parker et al (1968) The directional hearing is abnormal (Nordlund 1963) Parker also found a typical tone perversion in cases with brain stem lesions. Test results with distorted speech have shown (Bocca 1958 Calearo and Antonelli 1963 1968 Antonelli 1970a Jerger 1964 1970c) that low scores were obtained in the ipsilateral ear in patients with nuclear lesions, while involvement of the pathways after the crossing reduced the score of the contralateral ear The change in discrimination ability is often bilateral both for undistorted and distorted speech This is due to the fact that the cochlear nuclei are located so close to each other in the floor of the fourth ventricle that a tumour in this region can very easily impair hearing on both sides. In the four cases in this study the tumours were situated mainly to the right side of the brain stem and the scores for distorted speech were also much lower on the right side than on the left (see fig. 23) This indicates that the tumour had infiltrated mainly the right cochlear nuclei and had not grown rostrally in the region of the olivary complex. Similar results were obtained in the three other patients with brain stem tumours

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VI Summary

Central hearing disorders due to injuries in the central hearing pathways and auditory cortex cannot be revealed by ordinary tone and speech audiometry. With each cochlea bilaterally represented in the auditory cortex and with junctions at different levels, there is a high intrinsic redundancy in the hearing system. There is also a high extrinsic redundancy in undistorted speech, with superfluous information in the speech signals. However, by reduction of this information by various forms of distortions of the speech, hearing can be challenged and disturbances in the central hearing mechanism can then be diagnosed.

The aim of the present work was to design and standardize a new Swedish test material for distorted speech audiometry and to evaluate the effect of peripheral and central hearing disorders on the performance of these tests.

The distorted speech test battery comprised seven tests, viz., three forms of interrupted speech with 10, 7 and 4 interruptions/sec, two forms of time-compressed speech with speech rates of 220 and 290 wpm, respectively, frequency-distorted speech, and a test with competing speech.

Each test contained 100 sentences, distributed among four lists of equal length. One exception was frequency-distorted speech, where each list contained 17 sentences. The performance-intensity curves were based on 65 young persons with normal hearing, and the discrimination scores at 35 dB SL were above 90% in all tests except for interrupted speech with 4 interruptions/sec. When the test results were analysed according to the test sequence of the lists, it was found that practice had an effect on the discrimination of frequency-distorted speech, an observation which had not been known or taken into account in previous investigations. The first list in frequency-distorted speech was therefore used as a practice list. The other three lists were pooled and divided into two lists. The performance on distorted speech was also estimated on subjects, 50–60 years old, with normal hearing. A noteworthy finding was that in spite of normal hearing, as judged from the tone audiogram, the performance was not so good as by young normals. The tests also revealed that practice has a certain effect on all tests, which implies the elderly have to listen to a whole list to obtain reliable results, while young normals require only 7 or 12 sentences.

After standardization on 105 normals, the test battery included the test with 7 interruptions/sec., frequency-distorted speech, preceded by practice, time-compressed speech with the fastest speech rate, i.e., 290 wpm, and competing speech test. Examination of young persons with the whole test battery requires about 30 minutes. Examination of elderly patients, where two lists must be used in each test, requires 40–50 minutes.

The test battery was then used on patients with peripheral hearing loss. As expected, deteriorated hearing due to middle-ear changes had no effect on the test results. Provided that the intensity is raised enough to compensate for the attenuation in the middle ear, such hearing loss will not affect the results of distorted speech tests. In cochlear lesions, however, the test revealed that persons with acquired lesions found it very *difficult* to manage these tests. No such difficulty was encountered by patients with congenital cochlear lesions of the same magnitude.

In order to evaluate variations of the performance on distorted speech with the site of an intra-cranial lesion, thirty-three patients with brain injuries were tested. The patients were randomly distributed among four groups.

Twenty-six patients had temporal lobe lesions, either on the right side or on the left. None of those with left-sided injuries showed signs of aphasia.

Of those patients with temporal lobe lesions, the tumours presumably involved the auditory cortex in eleven. The results of tests with distorted speech showed large differences in performance between

cortex. The discrepancy noted between the ears however did not permit any conclusions about the location or extent of the lesions, either from the mean values calculated or from the results in the individual patient In the other groups the performance on both ears was largely equal The findings in this study are in agreement with those of Goldstein (1956) Bocca et al (1954 1955 1963) Jerger (1960 1964) and others.

In elderly patients there is often a decrease in discrimination of undistorted speech that is worse than might be expected from the tone audiogram. (Gaeth 1948 Pestalozza et al 1955 Schuknecht 1955 Hinchcliffe 1958 Glorig et al 1962 and others) This phenomenon is often referred to as phonemic regression" according to Gaeth, and is ascribed to degenerative changes in the central hearing pathways and cortex In this study seven patients in group I were 50–63 years old while the other four were younger The mean discrimination score on the ipsilateral ear was normal i.e., above 90 % in all patients This performance in discrimination thus indicates that age had no notable influence on the test results of ordinary speech test

When distorted speech audiometry was applied to patients with lesions involving the auditory cortex, there was found differences in discrimination between the ipsi and contralateral ears around 50 % with interrupted speech tests and time-compressed speech

Frequency-distorted speech showed the smallest differences between the ears as did competing speech test where the discrimination scores on the contralateral ear varied considerably

These findings are not in agreement with those of Bocca and his group (1963) Matzker (1959) Jerger (1960 1964 1970c) Kimura (1961) Feldmann (1964 1967) and others, who found frequency-distorted speech and different forms of binaural competing tests to be the most sensitive tool for revealing auditory cortical pathology

The differences between the results in this study and those reported by other authors can probably be explained by both differences in the test methods and languages used

In brain stem pathology the distorted speech tests were very sensitive for revealing disturbances in the cochlear nuclei and the ascending auditory pathways. The findings in this study are quite in agreement with those of Bocca et al (1963) Jerger (1964) Calearo and Antonelli (1968) Matzker (1959) and others. The distorted speech tests thus are a valuable complementary to other audiological tests for diagnosing brain stem lesions.

As expected the test results with distorted speech audiometry varied from patient to patient Even if the extent and location of the lesion could be classified fairly well it was difficult to evaluate concommitant effects of focal edema the degree of infiltrative growth of the tumours, displacement of normal structures raised intra-cranial pressure and probably also retrograde degeneration of the auditory pathways. With this in mind each case with an intra-cranial lesion must be regarded separately when evaluating the test results with distorted speech audiometry The mean discrimination scores shown in figs 25 27 and 29 are given just to facilitate a general survey of the findings obtained by low redundant speech tests.

CONCLUDING REMARKS

Ordinary audiometric tests, with pure tone and undistorted speech audiometry give very little if any diagnostic information about disturbances in the central hearing pathways and auditory cortex On the other hand the results with distorted speech tests clearly showed that intra-cranial lesions involving the auditory cortex and adjacent hearing pathways markedly reduce the performance on the ear contralateral to the lesion, compared with the results obtained by the ipsilateral ear Temporal lobe lesions not involving the auditory cortex gave normal test results In brain stem lesions, the ipsilateral ears achieved reduced scores on distorted speech audiometry indicating involvment of the cochlear nuclei on the same side

Even if the most sensitive tests for revealing central hearing disturbances seems to be interrupted speech tests and time-compressed speech it is evident from the cases illustrated in figs 1?–16 and 31–36 that no one test by itself can reveal a central auditory lesion A firm diagnosis requires evaluation of the results of four or five different forms of distorted speech tests

Distorted speech audiometry of the different forms standardized and used in this study thus demonstrate a substantial value for the purpose of diagnosing dysfunctions involving the auditory cortex central hearing pathways and brain stem

VI Summary

Central hearing disorders due to injuries in the central hearing pathways and auditory cortex cannot be revealed by ordinary tone and speech audiometry. With each cochlea bilaterally represented in the auditory cortex and with junctions at different levels, there is a high intrinsic redundancy in the hearing system. There is also a high extrinsic redundancy in undistorted speech, with superfluous information in the speech signals. However, by reduction of this information by various forms of distortions of the speech, hearing can be challenged and disturbances in the central hearing mechanism can then be diagnosed.

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After standardization on 105 normals, the test battery included the test with 7 interruptions/sec., frequency-distorted speech, preceded by practice, time-compressed speech with the fastest speech rate, i.e., 290 wpm, and competing speech test. Examination of young persons with the whole test battery requires about 30 minutes. Examination of elderly patients, where two lists must be used in each test, requires 40–50 minutes.

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Twenty-six patients had temporal lobe lesions, either on the right side or on the left. None of those with left-sided injuries showed signs of aphasia.

Of those patients with temporal lobe lesions, the tumours presumably involved the auditory cortex in eleven. The results of tests with distorted speech showed large differences in performance between

the ipsi and contralateral ears especially in the test with 10 interruptions/sec. and time-compressed speech. The smallest difference between the ears was found for frequency-distorted speech These results contrast with those obtained by Bocca and his group who found frequency-distorted speech to be the most sensitive test for revealing disturbances in the auditory cortex

Nine of the patients with temporal lobe injuries had lesions situated at some distance from auditory cortex i.e in the temporal pole The test results with distorted speech tests revealed no differences between ipsi and contralateral ears There were also six patients in whom the lesions were thought to be very close to the auditory cortex In these patients the mean difference between the ears in distorted speech tests was small as expected

Three patients had tumours situated in other parts of the hemispheres and in these too distorted speech audiograms were normal In four patients with mainly right-sided tumours in the brain stem distorted speech tests gave markedly reduced scores on the right ear These results suggest that it was mainly the cochlear nuclei on the same side that were injured

The results thus clearly showed that tests with distorted speech audiometry can reveal lesions involving the auditory cortex and the central hearing pathways but not injuries situated outside this fairly welldefined area When the case history and the results of common diagnostic tests indicate a lesion possibly involving the central auditory pathways and cortex, the distorted speech tests presented here can give a correct diagnosis already in the early stages of the disease

It is clear however that this category of patients are relatively few The above mentioned possibilities of diagnosing central hearing disturbances might prove useful in the elucidation of a much more extensive problem, i e of those dysfunctions in hearing which are embraced in the term presbyacusis. There is evidence suggesting that deterioration of hearing with advancing age comprises peripheral and central components which cannot be distinguished from each other by ordinary audiological tests

Zusammenfassung

Hörstörungen auf Grund von Schädigungen in den zentralen Hörbahnen und der primären Hörrinde können nicht mit Ton- und Sprachaudiometrie diagnostiziert werden. Bei normalem Sprechen liegt ein Überschuss von Information für den Hörenden vor. Eine Reduzierung dieser Information durch verschiedene Formen von Sprachdistorsion belastet die Hörfunktion und Störungen in dem zentralen Hörmechanismus können auf diese Weise diagnostiziert werden.

Die Zielsetzung der Arbeit war, neues schwedisches Sprachmaterial für erschwerte Sprachaudiometrie zu standardisieren und den Effekt der Auffassbarkeit dieser Teste bei peripheren und zentralen Hörschädigungen zu beurteilen. Die Testserien umfassen 7 verschiedene Teste: 3 Formen von aufgesplittertem Sprechen mit 10, 7 resp. 4 Unterbrechungen per Sekunde, 2 Formen von zeitkomprimiertem Sprechen mit einer Sprechgeschwindigkeit von 220 resp. 290 Worten per Minute, frequenzfiltriertes Sprechen und ein Sprechen mit "competing speech".

Jeder Test enthält 100 Sätze, verteilt auf 4 Listen von gleicher Länge. Eine Ausnahme macht frequenzfiltriertes Sprechen, wo jede Liste 17 Sätze enthält. Die verschiedenen Teste wurden bei 85 jungen Versuchspersonen mit normalem Gehör standardisiert. Die Auffassbarkeit bei 35 dB S.L. war über 90 % in allen Testen mit Ausnahme des aufgesplitterten Sprechens mit 4 Unterbrechungen per Sekunde. Als die Testresultate mit Rücksicht auf die Testordnung der Listen innerhalb jedes Tests analysiert wurden, fand man, dass Übung das Testresultat bei frequenzfiltriertem Sprechen beeinflusste.

Die Auffassbarkeit von erschwertem Sprechen wurde auch bei [illegible]0 Versuchspersonen im Alter von 50 bis 60 Jahren und mit normalem Gehör beurteilt. Ein bemerkenswerter Befund war, dass trotz normalen Gehörs laut Tonaudiogramm eine gesenkte Diskriminationsfähigkeit vorlag, verglichen mit jüngeren Normalhörenden. Die Untersuchungen machten auch deutlich, dass Übung einen gewissen Einfluss auf alle Teste hatte.

Nach der Standardisierung bei 105 Normalhörenden besteht die Testserie aus folgenden Versuchen: aufgesplittertes Sprechen mit 10 resp. 7 Unterbrechungen per Sekunde, frequenzfiltriertes Sprechen, zeitkomprimiertes Sprechen mit einer Sprechgeschwindigkeit von 290 Worten per Minute samt "competing speech" Test.

Wie erwartet zeigten Patienten mit peripherer Schwerhörigkeit auf Grund von Schädigungen im Mittelohr normale Testresultate. Wenn die Intensität lediglich erhöht wurde, um Schalleitungsstörungen zu kompensieren, wurde das Resultat der erschwerten Sprachaudiometrie nicht beeinflusst. Bei Innenohrstörungen zeigte es sich dagegen, dass Patienten mit erworbenen Innenohrstörungen eine sehr niedrige Auffassbarkeit von erschwertem Sprechen hatten. Derartige Schwierigkeiten zeigten sich nicht bei Patienten mit angeborenen Innenohrstörungen vom selben Schwierigkeitsgrad.

Um die Auffassbarkeit von erschwerter Sprachaudiometrie bei zentralen Hörstörungen zu beurteilen, wurden 33 Patienten mit intrakraniellen Tumoren getestet. Die Patienten wurden je nach der Lokalisation der Schädigung in 4 Gruppen aufgeteilt, und die Klassifizierung wurde von einem Neurochirurgen und einem Neuroradiologen vorgenommen. 26 Patienten hatten Temporallappenläsionen, entweder auf der rechten oder linken Seite. Keiner mit linksseitigen Störungen wies Zeichen von Aphasie. Bei 11 Fällen handelte es sich um Tumoren, welche die primäre Hörrinde betrafen. Die Resultate von Testen mit erschwerter Sprachaudiometrie zeigten sehr grosse Unterschiede in der Auffassbarkeit zwischen ipsi- und kontralateralem Ohr in dieser Gruppe, speziell für den Test mit 10 Unterbrechungen per Sekunde und zeitkomprimiertem Sprechen. Der kleinste

Unterschied zwischen ipsi – und kontralateralem Ohr zeigte sich bei dem frequenzfiltrierten Sprechen. Diese Resultate stehen im Gegensatz zu denen, Die Bocca und seine Gruppe fanden

9 der Patienten mit Temporallappenlasionen hatten Schadigungen, die auf Abstand von der primaren Horrinde lagen. Die Resultate von erschwerter Sprachaudiometrie zeigten in diesen Fällen keine Unterschiede zwischen ipsi – und *kontralateralem Ohr 6 Patienten hatten Schadigungen* im Temporallappen sehr nah bei der primaren Horrinde, und dort zeigten die Teste – wie erwartet – einen gewissen Unterschied zwischen ipsi- und kontralateralem Ohr

3 Patienten hatten Tumoren, die in anderen Teilen der Hemispharen lagen und diese hatten ebenfalls normale Auffassbarkeit von erschwertem Sprechen. Bei 4 Patienten mit hauptsachlich rechtsseitigen Tumoren im Bereich der Brucke zeigte die erschwerte Sprachaudiometrie markant gesenkte Werte auf dem rechten Ohr was für eine Schadigung kaudal der oberen Olivekerne spricht

Die Testresultate zeigen somit deutlich, dass erschwerte Sprachaudiometrie die Moglichkeit gibt Schadigungen, die die primare Horrinde und naheliegende zentrale Horbahnen umfassen, zu diagnostizieren dagegen nicht Schadigungen, welche ausserhalb dieses gut abgegrenzten Gebietes liegen Wenn auf Grund des Krankheitsverlaufes und gewohnlicher diagnostischer Untersuchungen Ursache vorliegt eine Schadigung, welche die zentralen Horbahnen und die primare Horrinde angreift zu vermuten so kann erschwerte *Sprachaudiometrie zeitig zu einer korrekten Diagnose* führen.

Es ist jedoch klar dass diese Kategorie von Patienten relativ klein ist. Die aufgezeigten Moglichkeiten, zentrale Horschädigungen zu diagnostizieren, deuten auf verbesserte Methoden die Schwerhorigkeit zu beurteilen welche in dem Begriff presbyacusis zusammengefasst ist.

Bei herabgesetztem Gehor das eine Folge hoheren Alters ist, gibt es Indikation auf einen variierenden Grad von sowohl peripheren wie zentralen Horstorungen, welche mit konventionellen audiologischen Testmethoden nicht von einander unterschieden werden konnen.

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Appendix

TEST LISTS (1–4) USED FOR TIME-COMPRESSED SPEECH WITH A SPEECH RATE OF 290 WPM

List 1 (1)

Lennart slog sönder det stora fönstret.
Han åker kanske till landet på söndag
Svenskarna trivs med solen i Spanien
Kalle dukade efter middagen.
Vattnet är ännu för kallt för bad
Måste jag läsa boken i kväll?
Tänder du lampan, så ser du bättre
Läxorna först och nöjena sedan
Våga inte komma för sent
Planen är full av gammalt lov
Kan du inte träffa prick?
Gråla inte på grannens barn
Hur många syskon har Lena?
Är du aldrig rädd för hunden?
Granen barrar före plak
Bruden har krona och långa handskar.
Lockigt hår är sött på småbarn
Hur lång är vägen till Stockholm
Svenska flaggan halades ombord
Vinden sliter alla segel
Bada gärna men inte i dammen
Göteborg har landets största hamn
Roddaren kämpade länge i båten
Cigarret förpestar luften i rummet.
Varför bråkar Göran och Pelle

List 2 (2)

Posten kommer varje dag
Räven plundrade fågelns bo
Tåget spårade ur i kurvan
Ost och vin är gott tillsammans.
Blommiga byxor är högsta mode
Bullar och mjölk är bra som mellanmål
Rött ljus hindrar trafiken
Kaffe på maten avslutar middagen.
Porten låses klockan tio
Glass är både gott och nyttigt.
Gubben laste en tidning på natten.
Kronor och ören är svenska mynt.
Italiens karta liknar en stövel
Höstens regn har skadat marken.
Billiga ljus brukar droppa och ryka
Bilar och cyklar trängdes på gatan.
Pojken ramlade och slog sitt knä.
Båtar och bryggor hör sommaren till.
Den nya terminen har just börjat
Vänta en stund så kommer doktorn.
Frisk luft och motion gör nytta.
Det härliga lövet är nästan slut.
Var snäll mot djuren du möter i skogen.
Skogen på landet är stadsbornas paradis
Annas syster säljer bilar

List 3 (3)

Lärkan är alltid välkommen gäst.
Grevinnan bar tunga halsband och ringar
Tårtan måste ha tio ljus.
Kola är inte bra för tänderna.
Alla stolarna skall målas blå
Kungar brukar bli mycket gamla.
Bomben sprängdes i luften i natt.
Mamma fick ont i öron och hals.
Många trivs med att vandra i fjällen.
Sommar ingår i skolans tränilag
Jag har beställt en vit telefon.
Varför är alla träd så gröna?
Måste du köpa en blommig klänning
Kan du visa mej vägen till Malmö
Gården är inte utsatt på kartan.
Tvätten torkar fort i solen.
Skramla inte med koppar och fat.
Golvet är nybonat och väldigt halt.
Du får gärna torka disken.
Spetsa öronen och lyssna noga.
Gumman säljer fisk på torget.
Farmor hade en schal om halsen.
Lägg en ren duk på bordet.
Tomten kommer till lydiga barn.
Hundarna sprang och lekte i solen.

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Appendix

TEST LISTS (1–4) USED FOR TIME-COMPRESSED SPEECH WITH A SPEECH-RATE OF 290 WPM

List 1 (1)

Lennart slog sonder det stora fonstret.
Han åker kanske till landet på sondag
Svenskarna trivs med solen i Spanien.
Kalle diskade efter middagen
Vattnet ar annu for kallt for bad
Måste jag läsa boken i kvall?
Tander du lampan, så ser du battre
Laxorna forst och notena sedan
Våga inte komma for sent
Planen ar full av gammalt lov
Kan du inte traffa prick?
Gråla inte på grannens barn
Hur många syskon har Lena?
Är du aldrig radd för hunden?
Granen barrar fore påsk
Broden har kroma och långa handskar.
Lockigt hår ar sött på småbarn
Hur lång ar vagen till Stockholm?
Svenska flaggan halades ombord.
Vinden sliter i alla segel
Bada gärna men inte i dammen.
Goteborg har landets storsta hamn
Roddaren kampade lange i båten.
Cigarrer förpestar luften i rummet
Varfor bråkar Goran och Pelle?

List 2 (2)

Posten kommer varje dag.
Raven plundrade fågelns bo
Tåget spårade ur i kurvan
Ost och vin ar gott tillsammans
Blommiga byxor ar hogsta mode
Bullar och mjolk ar bra som mellanmål
Rott ljus hindrar trafiken.
Kaffe på maten avslutar middagen
Porten låses klockan tio
Glass ar både gott och nyttigt.

Gubben laste sin tidning på natten.
Kronor och oren ar svenska mynt.
Italiens karta liknar en stovel
Hostens regn har skadat marken.
Billiga ljus brukar droppa och ryka.
Bilar och cyklar trangdes på gatan.
Pojken ramlade och slog sitt knä
Båtar och bryggor hor sommaren till.
Den nya terminen har just börjat.
Vanta en stund så kommer doktorn.
Frisk luft och motion gor nytta
Det harliga lovet ar nastan slut.
Var snall mot djuren du moter i skogen.
Stugan på landet ar stadsbornas paradis
Anitas syster saljer bilar

List 3 (3)

Larkan är alltid valkommen gast.
Grevinnan bar tunga halsband och ringar
Tårtan måste ha tio ljus.
Kola ar inte bra för tänderna.
Alla stolarna skall målas blå.
Kungar brukar bli mycket gamla.
Banken sprangdes i luften i natt.
Mamma fick ont i oron och hals.
Många trivs med att vandra i fjallen.
Simning ingår i skolans traning
Jag har bestallt en vit telefon.
Varfor är alla trad så grona?
Måste du kopa en blommig klanning?
Kan du visa mej vagen till Malmo
Gården är inte utsatt på kartan.
Tvatten torkar fort i solen.
Skramla inte med koppar och fat.
Golvet ar nybonat och valdigt halt.
Du får garna torka disken
Spetsa oronen och lyssna noga
Gumman saljer fisk på torget.
Farmor bade en schal om halsen.
Lagg en ren duk på bordet.
Tomten kommer till lydiga barn.
Hundarna sprang och lekte i solen.

List 4 (4)

Alla apelsiner har tjocka skal
Professorn glommer sina glasogon ofta
Dockan sover garna middag
Sås och potatis ar mat for barnen
Alla leksaker ligger på golvet
Hyllan sitter snett på vaggen
Samtalet stordes av bullret på gatan
Stugan ar rod med blåa knutar
Pojkarna spelar kula på gården
Musiken spelade så taket lyftes.
Forbjudet att leka på gatan flickor
Klockan visade tio i fyra.
Ljudet tranger inte fram.
Vid tre tiden kommer mamma hem.
Ficklampan lyste svagt i morkret
Backen i dalen svammade over
Bjornen har nyss vaknat ur idet
Bussens forare fick korkortet indraget
Våren ar redan långt på vag.
Smutsen på fonstren syns i solen
Maten har blivit valdigt dyr
Tvatta handerna och byt din skjorta
Ät upp all maten på tallriken.
Huset ar klatt med gult tegel
Passet måste skaffas i tid fore resan

TEST LISTS (5–8) USED FOR TIME-COMPRESSED SPEECH WITH A SPEECH RATE OF 220 WPM

List 5 (1)

Tradet blåste omkull i stormen
Fjallen lockar många turister
Lingonen brukar mogna i september
Doktorn tittade i båda oronen.
Saden står gul på åkern i torkan
Linjalen ar tre decimeter lång.
Båtarna har roda och grona segel
Honan varpte fyra agg
Bonderna onskar sig mycket regn
Groten var seg som Karlssons klister
Katten och råttan lekte tafatt
Sikten ar ganska skymd i kurvan.
Skruven har rostat fast i låset
På våren måste båten målas.
Grot och mjolk ar nyttig foda.
Rutigt och randigt ar modernt i år
Små barn sitter i knat
Hunden tar hand om sina egna valpar
Mamma tog sin dotter i orat
Eld och vatten ar gamla fiender
Den vackra tavlan hanger på vaggen
Kattungar ar blinda i nio dagar
Krokodiler ar mycket farliga djur
Klockan fyra går bussen till stan.
Tra upp den roda tråden på nålen

List 6 (2)

Getter klattrar bra i bergen.
Dorrklockan har en gall signal
Husthovarna lyser som solar på våren.
Hur många timmar finns på dygnet?
Kan du rakna till hundra redan?
Papper och penna finns framme på hyllan
Spårvagnen går från forort till centrum
I Goteborg ar samtliga bilar O-markta
Filmen med badbilderna har fastnat i tullen.
Den blåa vasen står i fonstret
Flickornas kjolar ar korta i år
Telefonen ar chefens standiga plåga
Kunden påstår att frukten ar rutten
Volvon korde forbi en lastbil
Klockan i kyrktornet slår varje timme.
Publiken gick mitt i forestallningen.
Musiken skvalade hela dagen
Affaren gick med stor forlust
Apan skalar sjalv bananen
Strutsen stack sitt huvud i sanden.
Tack for ditt långa och vanliga brev
Den roda lastbilen tutade plotsligt
Du ar ganska bra på kortet
Cirkusens elefant har blivit sjosjuk
Barnen får leka på den grona mattan

List 7 (3)

Tryck på knappen så ringer klockan
Vilka farger har danska flaggan?
Tyskar och fransman ar ganska lika
Tupparna slogs så fjadrarna rok
Påsken kommer tidigt i år
Den roda fargen syntes bra
Den gamla luffaren bodde i huset
Gubben led av en obotlig torst
Flickan kopte en lila kjol
Mamma kommer strax med maten
Koket var fullt av disk och buteljer
Gravning ar ett jobb for starka karlar
Vaskan var full med mat och flaskor
Flickan knot ett band om

Elden brann och sprakade i spisen.
Två båtar mottes i sundet.
Pojken bloder ofta naasblod
Hunden skaller på grannens barn.
Målaren anvande felaktig färg
Fågeln satt och kvittrade i buren
Flickan har fått en ny magister
Morfar spelar på operan i kvall
Pojkarna åkte skridsko på isen.
Brudgummen hade rod ship till fracken
Torpet hade blommor och gras på taket

List 8 (4)

Barnen ar lediga från skolan idag
Laxor och TV skapar problem
Gumman var fortjust i roda blommor
Att roka ar både dyrt och farligt
Blått och rott ar vårens modefarg
Tåget kom en timme for tidigt
Mormor blev sjuk och gick till doktorn
Kvinnan satt parken och solade
Birgitta har hyrt en omodern lagenhet
Rikligt med fisk satt fast i garnen
Rosor bor tackas med granris pa våren
Klockan i tornet gick alltid for sakta
Att fiska kraftor ar en trevlig syssla
Pias docka har brunt hår
Programmen i TV slutar for sent
For mycket kaffe ger besvar med magen
Barnens biffar var branda och sega
Brevbararens vaska var stor och tung
Vackarklockan låter illa på morgonen
Fotografen tyckte att kameran var lamplig
Polisen tappade sin mossa striden
Infodingen bygger sjalv sin kanot
Pumpen på gården hade rostat på vintern
Ungkarlen levde på ol och konserver
Stadfrun kommer varje vecka

TEST LISTS (9-12) USED FOR INTERRUPTED SPEECH WITH 4 INT/SEC

List 9 (1)

Moster lade stickat en drakt till babyn
Det franska koket har utmarkt rykte
Kallskankan skar sig fingret med kniven.
Grodan tog långa skutt diket
Flickan korde standigt på provet.
Far laser hogt for sin flicka
Kost och logi ingick i lonen.
Barnet soker trost i nappen.
Pojkarna sparkade boll på planen
Foraren stannade bilen på gatan
Elektrisk rakning går latt och smartfritt.
I tradgården hanger tvatten till tork.
Ena bordsbenet gick sonder på festen.
Skorna var nya och alldeles for tränga.
Rånarna kastade vaskan i sjon.
Biljetterna till bion tog slut i forvag.
Farfar måste stodja sig på kappen.
Laget tranar varje kvall
Pojkarna spelar kula på gården.
Gruppen består av dragspel och gitarr
Konstnaren ser naturen i grått.
Frukter och bar ar godast på hosten.
Snon och kylan kom tidigt i år
Hostens färger ar rott och gult
Kalvarna råmar muntert i solen

List 10 (2)

Hamnen doftar tjara och farg
Klipporna vid kusten ar hala och gråa
Vågorna slog hogt over bryggan i stormen
Trad och buskar gronskar redan
Kaptenen stod på dack och vinkade
Bilar och bussar trangs på gatan.
Papper och glas ska kastas i tunnan.
Dockan Lisa har rutig kappa
Svart rok valler ur skorstenen
Spanjorens brev kom med flaskpost
Lillan alskar sagan om hasten
Reklam radio ar forbjudet i Sverige.
Apparaten drar for mycket strom
Bilens dack ar mycket slitna.
Pelles vante har hål på tummen.
Flickan rodde båten over sjon.
Foraldrar och barn har olika åsikter
Arbetet varar från måndag till fredag
Grannens baby har blåa ogon
Kerstins kofta har blivit for liten
Kungens fodelsedag ar i november
Mammas kottbullar ar alltid godast.
Graset vaxer hogt och tatt.
Isen kan omojligt bära en vuxen.
Varma smorgåsar ar gott som kvallsmål

List 11 (3)

Bussen stannar borta vid hornet.
Fisken blev storre for varje dag.

List 4 (4)

Alla apelsiner har tjocka skal
Professorn glommer sina glasogon ofta
Dockan sover gärna middag.
Sås och potatis ar mat for barnen
Alla leksaker ligger på golvet
Hyllan sitter *snett på vaggen.*
Samtalet stordes av bullret på gatan.
Stugan ar rod med blåa knutar
Pojkarna spelar kula på gården
Musiken spelade så taket lyftes.
Forbjudet att leka på gatan flickor
Klockan visade tio i fyra
Ljudet tranger inte fram.
Vid tre tiden kommer mamma hem.
Ficklampan lyste svagt i morkret
Backen i dalen svammade over
Bjornen har nyss vaknat ur idet
Bussens forare fick korkortet indraget
Våren ar redan långt på vag.
Smutsen på fonstren syns i solen.
Maten har blivit valdigt dyr
Tvatta handerna och byt *din skjorta*
Ät upp all maten på tallriken
Huset ar klatt *med gult tegel*
Passet måste skaffas i tid fore resan

TEST LISTS (5–8) USED FOR TIME-COMPRESSED SPEECH, WITH A SPEECH RATE OF 220 WPM

List 5 (1)

Tradet blåste omkull i stormen
Fjallen lockar många turister
Lingonen brukar mogna i september
Doktorn tittade i båda oronen
Saden står gul på åkern i torkan
Linjalen ar tre decimeter lång.
Båtarna har roda och grona segel
Honan varpte fyra agg
Bonderna onskar sig mycket regn
Groten var seg som Karlssons klister
Katten och råttan lekte tafatt
Sikten ar ganska skymd i kurvan
Skruven har rostat fast i låset
På våren måste båten målas.
Grot och mjolk ar nyttig foda
Rutigt och randigt ar *modernt i år*
Små barn sitter i knat
Hunden tar *hand om sina egna valpar*
Mamma tog sin dotter i orat
Eld och vatten ar gamla fiender
Den vackra tavlan hanger på vaggen
Kattungar ar blinda i nio dagar
Krokodiler ar mycket farliga djur
Klockan fyra går bussen till stan.
Tra upp den roda tråden på nålen.

List 6 (2)

Getter klattrar bra i bergen
Dorrklockan har en gall signal
Hasthovarna lyser som solar på våren.
Hur många timmar finns på dygnet?
Kan du rakna till hundra redan?
Papper och penna finns framme på hyllan
Spårvagnen går från *forort* till centrum
I Goteborg ar samtliga bilar O-markta
Filmen med badbilderna *har* fastnat i tullen
Den blåa vasen står i fonstret.
Flickornas kjolar ar korta i år
Telefonen ar chefens standiga plåga
Kunden påstår att frukten ar rutten
Volvon korde forbi en lastbil
Klockan i kyrktornet slår varje timme
Publiken gick mitt i forestallningen
Musiken skvalade hela dagen
Affaren gick med stor forlust
Apan skalar sjalv bananen
Strutsen stack sitt huvud i sanden.
Tack for ditt långa och vanliga brev
Den roda lastbilen tutade plotsligt
Du ar ganska bra på kortet
Cirkusens elefant har blivit sjosjuk
Barnen får leka på den grona mattan

List 7 (3)

Tryck på knappen så ringer klockan
Vilka farger har danska flaggan?
Tyskar och fransman ar ganska lika
Tupparna slogs så fjadrarna rok
Påsken kommer tidigt i år
Den roda fargen syntes bra
Den gamla luffaren bodde i huset
Gubben led av en obotlig torst
Flickan kopte en lila kjol.
Mamma kommer strax med maten
Koket var fullt av disk och buteljer
Gravning ar ett jobb for starka karlar
Vaskan var full med mat och flaskor
Flickan knot ett band om håret

Tvätta händerna i tvål och vatten
Vanern ar Sveriges storsta sjo
Böckerna står tätt i biblioteketes hylla.
Skridskorna behöver slipas ofta
Storken är en sällsynt fågel i Skåne
Regnet föll i häftiga skurar.

List 15 (3)

Potatisen blommar redan på fälten.
Slå inte spiken för hårt i väggen
Björkarna är gula i mitten av september
Körsbären hängde i stora klasar
Apelsinerna kommer från södra Spanien
Flygplanet kretsade lågt över målet
Arkeologen hittade krukor i sanden.
Läraren rot på taket sprack
Kungen har bott i slottet sommar
Cykling och tennis ger god motion
Kaffet från Brasilien är världens bästa
Lillan är knappast lik sig på fotot
Farmor har fått ett vykort från pappa
Barnen fick lov för läraren var sjuk.
Lotta fick mata björnarna på Skansen.
Hostela är lite bättre idag
Lång hår är vanligt på pojkar
Glassen smälter snabbt i solen
Spöken finns på gamla slott
Alla teatrar har stängt på sommaren
Saft och bullar är gott i värmen
Lillan har lärt sig simma sommar
Barnen dansar kring granen på jul
Bagarens barn äter gärna bröd
Pappa kommer hem till middagen

List 16 (4)

Hunden skäller på alla grannar
Dagen firades med klang och jubel
Ha alltid nål och tråd i väskan
Olle och pappa målar huset
Lasse somnade på första lektionen
Kalle läste sina läxor slarvigt
Lisa ritar tjocka gubbar
Granen kan bl väldigt hög
Jorden är nästan rund som en boll
Kajsa grät när ballongen sprack
Orkestern spelar sorglig musik
Radion har gått sönder igen
Varje söndag är det fotboll på TV
Bollen åkte över planket
Bilen körde ner diket

Gungorna i parken är alldeles för höga
Dimman sänkte sig över kanalen.
Regnet skvalar och himlen är grå
Ett vitt sken syntes id horisonten
Grannens pojke är smutsig om fötterna
Vasen ramlade i golvet och sprack
Bladen är redan alldeles torra.
I morse vaknade jag klockan fem.
Farbrorns kapp är svart och krokig.
Svenskarna badar gärna i södern

TEST LISTS (17– 0) USED FOR INTERRUPTED SPEECH WITH 10 INT/SEC

List 17 (1)

Stina har bränt sin rygg i solen
Mjölken rann över hela golvet
Solen har blekt mina bästa gardiner
Spegeln i hallen hänger snett
Kampanjen avslutas redan på söndag
Valet skedde i slutet av augusti
Lejonet rot så buren skakade.
Den klara rösten hördes långt
Lamporna lyser knappast av sig själva
Peppar och papper finns på bordet.
Trädgårdsarbete ger hårda och valkiga händer
Evas kjol r randig på tvären
Maja har en maska på höger strumpa
Båten rullade kraftigt i stormen
Lillan fick en docka i julklapp
Skorstenen är femtio meter hög
Flaggstången målades gul i fjol
Karin arbetar på avdelning tolv
Syster bjöd på kaffe efter maten
Soffan är både bekvam och billig
Socker är inte nyttigt för tänderna
Kaminens oron står rakt upp.
Resultaten av proven är helt *perfekta*.
Bilföraren går med armen i band
Varför får jag inga brev?

List 18 (2)

Askan spreds över hela bordet
Skatten blir högre för varje år
Ärterna förekom glest i soppan
Fläsk och potatis är fettrik föda
Doften av kaffe spred sig i huset
Gamla strumpor luktar illa.
Här finns kor men inga kalvar
De små slantarna skramlar i fickan

Bilen körde på fyra hjul.
Saxen behöver verkligen slipas.
Karin hörde att bilen tutade
Studenterna hälsar våren med sång.
Träden växte vid den lugna dammen.
Dammet hopar sig på översta hyllan
Kan du inte skriva läsligt
Morfar har ett grävitt skägg
Vägen till Stockholm är backig och krokig.
Paris broar lockar turister
Priserna stiger för varje år
Resan till södern varade en månad
Lokalen är fullsatt varje kväll
Mopeden hörs i hela kvarteret
Ormen ringlade i det höga gräset
Katten lapade den varma mjölken
Lillan leker med spann och spade
Det är skönt när kastan stammer på kvällen
Frysboxen var trasig hela vintern
Skidorna gled och Peter ramlade
Det nya klistret fäster på allt.
Varuhuset öppnar med stor visning
Utställningen reser omkring i Sverige

List 12 (4)

Katalogen blir tyngre för varje år
Ulla blev instängd när dörren stängdes.
Arbetarna river huset på höjden
Väldiga stenar spärrade vägen.
Eva har tappat nyckeln till cykeln
Tejp är bra till nästan allt
Varför är kattens ögon gröna?
Gräsmattan borde klippas var vecka.
Tarzan och Fantomen är pojkens idoler
Fiol och trumpet är gamla instrument
Vägen visade alldeles fel.
Loppor är ganska sällsynta djur
Kerstin har klämt sin vänstra tumme
Hela stugan är full av ungar
Älgen sprang rakt över vägen
Flickans röda strumpor lyste
Du har tappat klacken på skon
Tre båtar seglade samtidigt
Kalaset slutade efter midnatt
Vill du ha fläsk till middag jämt?
Från vilken perrong går tåget till Oslo?
London är Europas största stad
Pojken och flickan sprang i kapp
Gubben i månen log i smyg
Domaren blåste länge i pipan

TEST LISTS (13–16) USED FOR INTERRUPTED SPEECH WITH 7 INT/SEC.

List 13 (1)

Japanska kameror är ganska billiga.
Hatten blåste bort i stormen
Snögubben har tappat fyra knappar
Pipan hänger snett i munnen
Hunden och katten leker på golvet
Har du glömt att du spelar i kväll?
Gumman sålde en korg med blommor
Ljuset brinner med flammande låga
Berget är klätt med mossa och slippor
Katten har gömt sina ungar för räven
Lasse och Olle fick stryk av magistern
Björkarna skiftar i lila på våren.
Stoppa inte kniven i mun
Yxan måste slipas för att fälla trädet
Åskan har slagit ner i eken.
Snödropparna blommar redan i Skåne
Att parkera sin bil är svårt i staden.
Göken gol någonstans i väster
Jönköping ligger vid Vätterns sydspets.
Maskrosorna lyser gult i solen
Maneterna bränns, om man kommer för nära
Åskan ekade mellan bergen
Ekot svarade uppifrån fjället
Hunden och katten leker tillsammans
Taxibilen väntade länge på gatan

List 14 (2)

Det är alldeles för varmt att sitta i buss
Turisterna finns på alla badorter
Ystad är Sveriges sydligaste stad
Nyckeln passar inte i låset.
Den blåa byrån passar mot tapeten
Vilken härlig vilstol du köpte
Bilen fick en buckla på skärmen
Lillan har tappat sin första tand
Målaren har stavat fel på skylten
Städerna ligger tätt i Holland
Bänkarna i parken målades i april
Banken stänger klockan fem
Rånet i England är nyligen uppklarat
Lillen har inget hår på huvudet
Tullen hittade flera flaskor
Tjuven stal hela dagskassan
Tiggaren fick pengar till mat och öl
Musikanten spelade en gammal polka
Negrernas fötter är vita på undersidan

Tvätta händerna i tvål och vatten.
Vänern är Sveriges största sjö
Böckerna står tätt i bibliotekets hylla
Skridskorna behöver slipas ofta
Storken är en sällsynt fågel i Skåne
Regnet föll i häftiga skurar

List 15 (3)

Potatisen blommar redan på fälten
Slå inte spiken för hårt i väggen
Björkarna är gula i mitten av september
Korsbären hängde i stora klasar
Apelsinerna kommer från södra Spanien
Flygplanet kretsade lågt över målet
Arkelogen hittade krukor i sanden
Läraren rot så taket sprack
Kungen har bott i slottet i sommar
Cykling och tennis ger god motion.
Kaffet från Brasilien är världens bästa
Lillan är knappast lik sig på fotot
Farmor har fått ett vykort från pappa
Barnen fick lov för läraren var sjuk.
Lotta fick mata björnarna på Skansen
Hörneln är inte bättre idag
Lång hår är vanligt på pojkar
Glassen smälter snabbt i solen
Spöken finns på gamla slott
Alla teatrar har stängt på sommaren
Saft och bullar är gott i värmen
Lillan har lärt sig simma i sommar
Barnen dansar kring granen på jul
Bagarens barn äter gärna bröd.
Pappa kommer hem till middagen.

List 16 (4)

Hunden skäller på alla grannar
Dagen firades med klang och jubel
Ha alltid nål och tråd i väskan
Olle och pappa målar huset
Lasse somnade på första lektionen
Kalle lärde sina läxor slarvigt
Lisa ritar tjocka gubbar
Granen kan bli väldigt hög.
Jorden är nästan rund som en boll
Kajsa grät när ballongen sprack.
Orkestern spelar sorglig musik.
Radion har gått sönder igen
Varje söndag är det fotboll på TV
Bollen åkte över planket
Bilen körde ner i diket

Gungorna i parken är alldeles för höga
Dimman sänkte sig över kanalen
Regnet skvalar och himlen är grå
Ett vitt skepp syntes vid horisonten.
Grannens pojke är smutsig om fötterna
Vasen ramlade i golvet och sprack.
Bladen är redan alldeles torra
I morse vaknade jag klockan fem.
Farbrors kapp är svart och krokig.
Svenskarna badar gärna i söder.

TEST LISTS (17–20) USED FOR INTERRUPTED SPEECH, WITH 10 INT/SEC

List 17 (1)

Stina har bränt sin rygg i solen
Mjölken rann över hela golvet
Solen har blekt mina bästa gardiner
Spegeln i hallen hänger snett.
Kampanjen avslutas redan på söndag
Valet skedde i slutet av augusti
Lejonet röt så buren skakade
Den klara rösten hördes långt.
Lamporna lyser knappast av sig själva
Penna och papper finns på bordet
Trädgårdsarbete ger hårda och valkiga händer
Evas kjol är randig på tvären
Maja har en maska på höger strumpa
Båten rullade kraftigt i stormen
Lillan fick en docka i julklapp
Skorstenen är femtio meter hög
Flaggstången målades gul i fjol
Karin arbetar på avdelning tolv
Syster bjöd på kaffe efter maten.
Soffan är både bekväm och billig.
Socker är inte nyttigt för tänderna
Kaminens rör står rakt upp
Resultaten av proven är helt perfekta.
Bilföraren går med armen i band
Varför får jag inga brev?

List 18 (2)

Askan spreds över hela bordet
Skatten blir högre för varje år
Ärterna förekom glest i soppan.
Fläsk och potatis är fettrik föda
Doften av kaffe spred sig i huset
Gamla strumpor luktar illa
Här finns kor men inga kalvar
De små slantarna skramlar i fickan.

Goteborg ar Sveriges basta stad
Eva har ingen rosett i håret.
Stigen slingrade sig under traden
Stenarna rullade nerfor backen.
Torne trask ligger i Stockholm
Hyllorna nådde anda till taket
Taxen Karo har lång svans.
Blacket i pennan tog slut i går
Sirenen tjot så det ekade mellan husen
Orden trillade som parlor ur munnen
Äggen ramlade i gatan men holl
Tavlan forestaller sol och hav
Slottet i backen ar nyligen vitmålat
Kunden betalar reklamen for varan
Hungern slet i magen på vargen
Englands drottning har fyra barn
Moblerna på terrassen ar flatade av pil

List 19 (3)

Han paddlade kanot runt hela kusten
Takpannorna blåste ner i den svåra stormen
Valpen gnyr både dag och natt
Kattungen rev sonder de nya gardinerna
Tio huvuden syntes i dorren
Veckan har bara en enda fridag
Din nya sang ar alldeles for mjuk
Flickan har roda rosetter i flatorna.
Klockan ringer nar rasten ar slut
Kop en tvål nar den gamla ar slut
Bilden visar en rutig hatt
Tuta i luren nar tåget ska gå
En skruv saknas i den nya lampan
Blåklockor ingår i sommarens flora
Farfars bil har vant i diket
Hur många elever går i forsta klass?
Vill du hjalpa mig att lagga lakan?
Doktorn sager att du har ont i magen.
Äpplet ar moget och alldeles gront
De forsta hallonen smakar bast
Måste bilar drivas med olja
Gamla filmer visas i TV
Ringen låg i smutsen och blankte
Nalle har tappat ena ogat
Orkar du gå den långa vagen?

List 20 (4)

Dockan Lisa har rutig klanning.
Bilens ena hjul ar trasigt
Hjulet på cykeln fick punktering i går
Grannens barnvagn ar årets modell
Knyt ett band om ditt långa hår!
Bjorken har tappat alla bladen
Halka inte på barnens kulor!
Kartan tacker många lander
Smutsiga skor skall stallas i hallen
Backen mynnar i den grunda viken
Sladden racker lagom runt rummet
Farbrorn stodde sig på sin fina kapp.
Hasten skall hållas i strama tyglar
Reta aldrig andras djur
Forsok att tanka på något annat
Husvagnen hindrar trafiken på sommaren.
Bussen går var tionde minut
Sverige vann over Danmark i fotboll
Jag får skavsår av de nya skorna
Måste du gå till skolan redan?
Rosorna blommar tidigt på våren
Pelle badade ofta i havet
Pojken var radd for den svarta tjuren.
Tåget gick till Malmo och Lund
Flickan borstade tanderna ofta

TEST LISTS (21–22) USED FOR FREQUENCY DISTORTED SPEECH

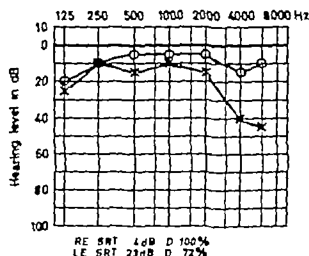
List 21 (1)

Solen varmer skont på sommaren
Barnen leker ute på angen
Gossen cyklar till skolan varje dag
En gammal man foll omkull på vagen
Det ar halsosamt att dri ka mjolk
Hunden blev radd och gomde sig
Far gav henne ett par nya skor
Vi måste rensa bort ograset
Brevlådan tommes flera gånger om dagen
Flickan blev sjuk och måste stanna hemma
Stockholm ar en va ker stad
Det har regnat mycket idag.
De flesta manniskorna dricker kaffe på morgonen
Potatis ska kokas innan den ates
Det ar skont att ta en lång promenad
Fågeln kom med mat åt ungarna
Gossen cyklar till skolan
Gråsparven blev radd och flog
Det har regnat hela natten
Mamma mår inte bra
Lillan vill leka med dockan
Flickan sitter och laser i en sagobok
Jag tycker om kottbullar
Många manniskor ater grot på kvallen
Far gav bort ett par nya skor

List 22 (2)

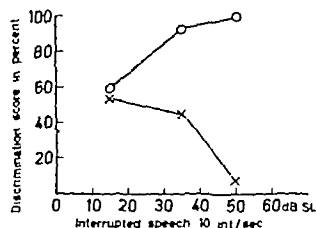
Hunden bor i en koja.
Spring och kop en tidning.
Det finns vackra blommor i tradgården
Det ar skont att bada.
Vi har en stuga på landet.
Kan du hamta ett paket åt mig.
På bordet står ett glas mjolk.
Mormor reser till Stockholm idag.
Barnen cyklar till skolan.
Vem springer på vagen?
Pojken fick ett par nya skor
Mamma steker kottbullar

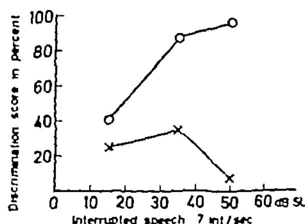
Gråsparven ar en liten fågel
Till frukost ater vi grot
Far kopte en fin docka åt lillan.
Det ar roligt att bada.
I natt har det regnat.
Jag bor i en gammal stuga på landet.
Froken laser ur boken.
Flickan leker med hunden i tradgården
Många manniskor dricker kaffe
Hamta tidningen som ligger i brevlådan
Det finns ett paket i min vaska.
Tåget går snart från stationen.
Flickan sitter och laser i en bok.

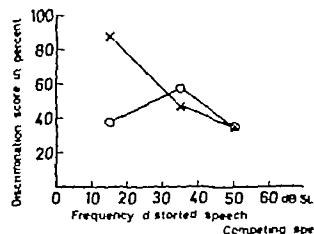


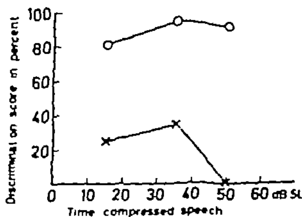
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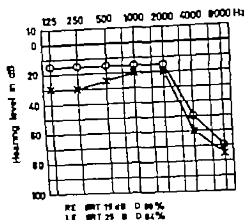




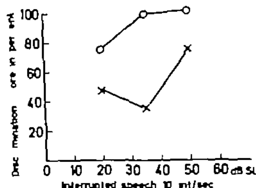
Competing speech RE 96% LE 96%

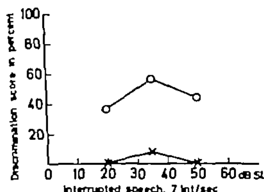
Fig. 31. Test results obtained with ordinary and distorted speech audiometry in a patient with glioblastoma in the right temporal lobe. The tests were performed 14 days after operation.
Dotted area denotes removed tumour.

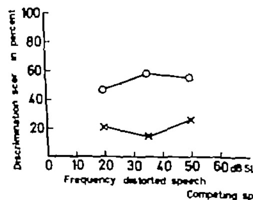
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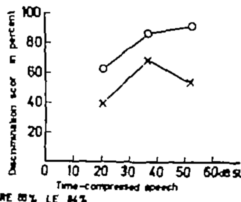






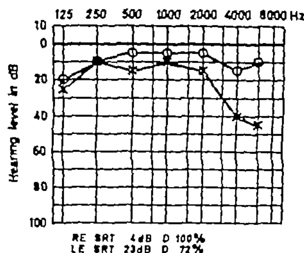




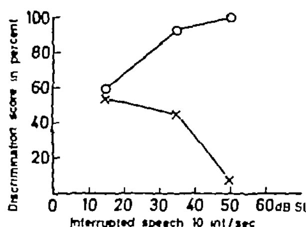


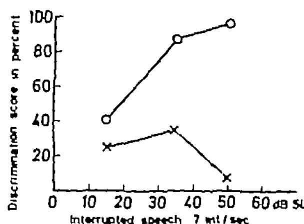
Competing speech RE 88% LE 84%

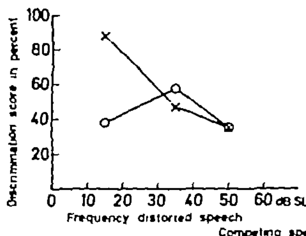
Fig. 52 Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe. The tests were performed 7 days after operation.
Dotted area denotes removed tumour
Broken lines denote edema

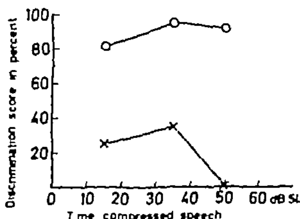








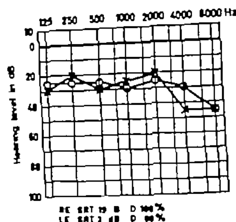




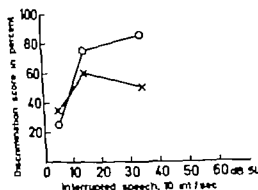
Competing speech RE 98% LE 96%

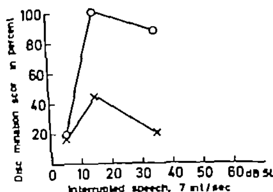
Fig. 31. Test results obtained with ordinary and distorted speech audiometry in a patient with a glioblastoma in the right temporal lobe. The test were performed 14 days after operation.
Dotted area denotes removed tumour.

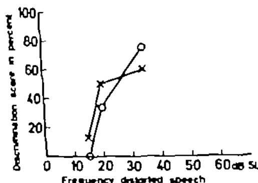
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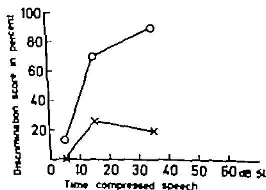
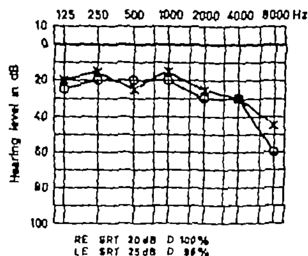
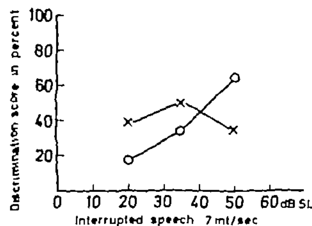
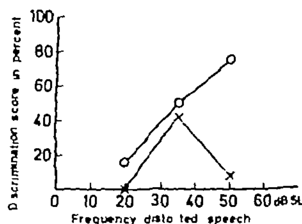


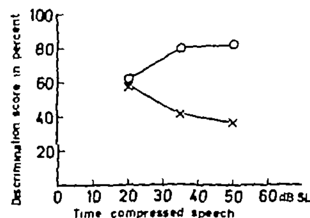
Fig. 34. Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe. The tests were performed 40 days after operation.
Dotted area denotes removed tumour.





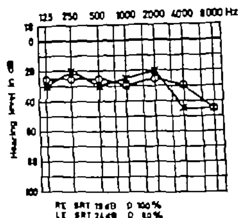






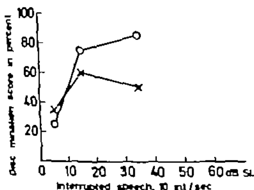
Competing speech RE 92% LE 82%

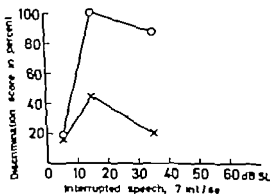
Fig. 33. Test results obtained with ordinary and distorted speech audiometry in a patient with a glioblastoma in the right temporal lobe. The tests were performed 5 days before operation.
Dotted area denotes extent of the tumour.

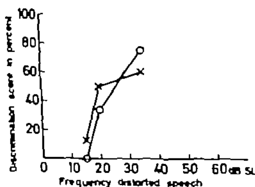


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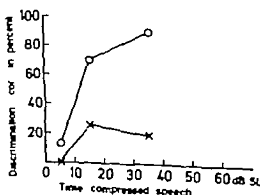
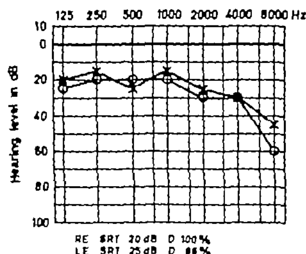
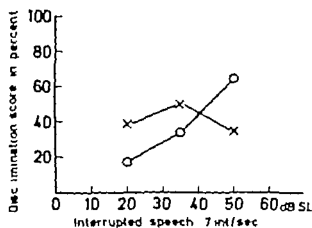
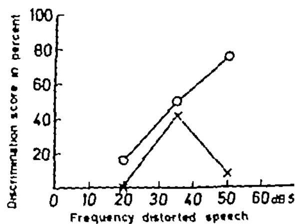


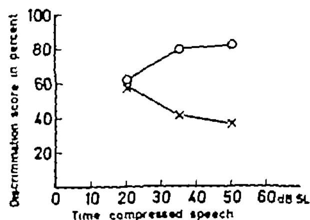
Fig. 34. Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe. The tests were performed 40 days after operation.
Dotted area denotes removed tumour





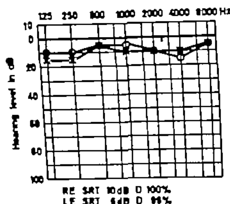




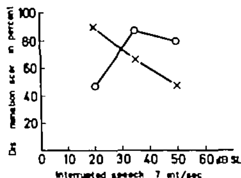


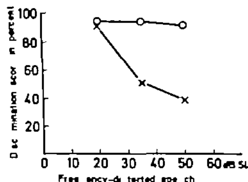
Competing speech RE 92% LE 52%

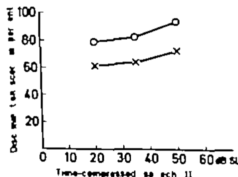
Fig 33 Test results obtained with ordinary and distorted speech audiometry in patient with a glioblastoma in the right temporal lobe The tests were performed 5 days before operation
Dotted area denotes extent of the tumour





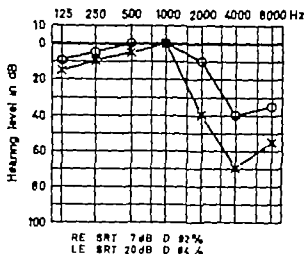




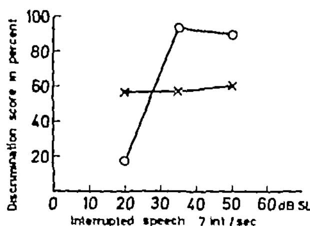


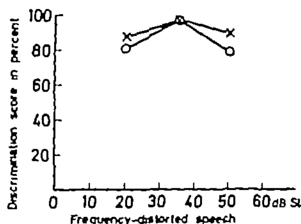
Competing speech RE 98% LE 84%

Fig 36 Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe The patient had been operated upon several times and the tests were performed in connection with X ray examination, which revealed recurrence of the tumour
Dotted area denotes removed tumour









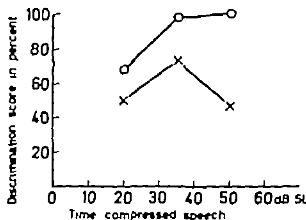
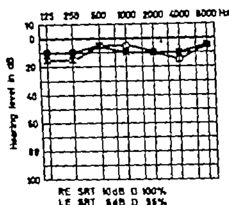


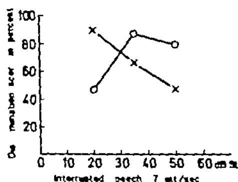
Fig 35 Test results obtained with ordinary and distorted speech audiometry in patient with a glioblastoma in the right temporal lobe The tests were performed 5 days before operation

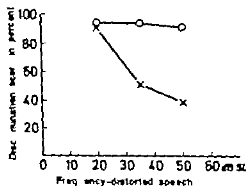
Dotted area denotes extent of tumour

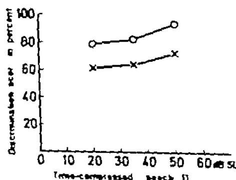
Broken lines denote edema





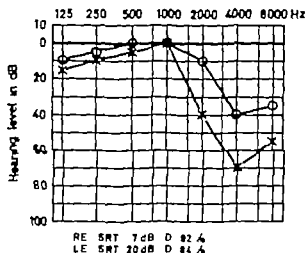






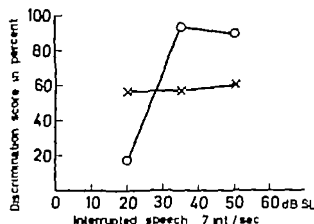
Competing speech RE 96% LE 84%

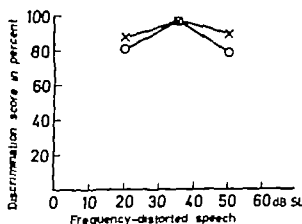
Fig. 36. Test results obtained with ordinary and distorted speech audiometry in patient with glioblastoma in the right temporal lobe. The patient had been operated upon several times and the tests were performed in connection with X-ray examination, which revealed recurrence of the tumour.
Dotted area denotes removed tumour.



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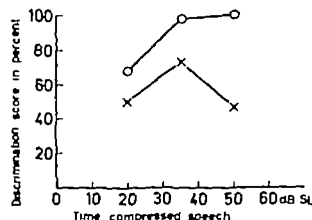


Fig. 35. Test results obtained with ordinary and distorted speech audiometry in patient with a glioblastoma in the right temporal lobe. The tests were performed 5 days before operation.
Dotted area denotes extent of tumour.
Broken lines denote edema.

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SUPPLEMENT 312

Deafening Effects of Impulse Noise on the Rhesus Monkey

from

The US Army Medical Research Laboratory
Fort Knox, Kentucky USA

and

The Inner Ear Research Laboratory
Case Western Reserve University Medical School
Cleveland, Ohio, USA

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SUPPLEMENT 312

Deafening Effects of Impulse Noise on the Rhesus Monkey

f om

The US Army Medical Research Laboratory
Fort Knox Kentucky USA

d

The Inner Ea Research Laboratory
C se W stern Reserve Uni ersity Medical School
Cleveland Ohio USA

CONTENTS

Foreword

The behavioral investigations reported in this monograph were conducted by CPT George Luz (Ph D) LTC John Fletcher (Ph D) and Dr James Mosko at the Experimental Psychology Division of the US Army Medical Research Laboratory Fort Knox, Kentucky 401 1 Professor Michel Loeb (Ph.D) of the University of Louisville initiated the project Techni l assistance was provided by Mr Carl Guthrie and animal testing was done by Mr William Cooper and Mr David Duffy Ear surgery was performed by Maj William Fravel M D of the Ireland Army Hospital Fort Knox Also closely involved with the project were Dr George Harker Director of the Experimental Psychology Division and COL Nichola Conte M D Commanding Officer of the Med cal Research Laboratory of Fort Knox

The sacrifice and initial histological preparation of the subjects were carried out at Fort Knox by Drs Kazuo Chiba M D and Armando Jimenez, M D Histological preparation was continued at the Inner Ear Research Laboratory at Case-Western Reserve University Medical School Cleveland Ohio through a grant from the John A Hartford Foundation Inc. New York City (C W R U 642 5822) Final histological analyses were carried out by Drs Marilyn Pinheiro Kazuo Chiba and Valdemar Jordan M D Director of the Inner Ear Research Laboratory

Because this monograph covers the activities of two independent laboratories the three major sections have been treated as separate studies each with a different set of authors However the table of contents the bibliography and the figure numbers are used to reference all three studies as a single monograph

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Uppsala 1973

The Relation Between Temporary Threshold Shift and Permanent Threshold Shift in Rhesus Monkeys Exposed to Impulse Noise

by George A Luz John L. Fletcher [2] William J Fravel [3] James D Mosko[1]

INTRODUCTION

If an ear shows a measurable but reversible loss in sensitivity after known exposure to sound the loss is called temporary threshold shift (TTS). The TTS is commonly measured (in decibels) at 2 min after termination of the sound (TTS_2) A number of similarities have been observed between TTS_2 and permanent threshold shift (PTS) For example Glorig, Ward & Nixon (1961) noted that the TTS_2 at 4 kHz acquired at the end of a working day in a noisy plant seemed to be of the same magnitude as the PTS seen after nine years on the job Additional similarities between TTS and PTS have been noted by Kryter (1970)

Such apparent relationships between TTS and PTS have led several investigators to probe another hypothesis—that an individual's susceptibility to TTS is an adequate predictor of his susceptibility to PTS A number of animal studies have tested this hypothesis. All have failed to support it. Among the animals studied have been the cat (Miller Watson & Covell 1963) the rat (Herman & Clack, 1963) the rhesus monkey (Harris 1967) and the chinchilla (Ward & Nelson 1968)

Generalizing from later research these past failures were reasonable Temporary threshold shift from any particular noise exposure cannot be used as an index of an ear's general susceptibility to fatigue (Ward 1971) For example an ear's susceptibility to TTS from low frequency noise does not adequately predict its susceptibility to high frequency noise (Ward 1968) and its susceptibility to noise at one intensity may not predict its susceptibility at a higher intensity (Kryter 1970 p 168) At best TTS could only be used to pick out the most susceptible individuals within a given noise environment (e.g Pfander 1968 1969). Even this relationship has not been firmly established. Thus more studies are needed

As a test of the correlation between initial susceptibility to TTS and later susceptibility to PTS from a single noise source 10 rhesus monkeys were given behavioral audiograms and exposed repeatedly to impulse noise. After each exposure subjects were tested until recovery from TTS was complete Permanent threshold shift was measured 64 days after the last exposure

METHOD

Subjects

Eleven feral rhesus macaque monkeys were available as subjects. The oldest, a 10-year-old male could not be trained Of the

Experimental Psychology Division, US Army Medical Research Laboratory Fort Knox Kentucky 40121 USA

Present Address Department of Psychology Memphis State University Memphis, Tennessee 38111

ENT Chief Ireland Army Hospital, Fort Knox, Kentucky 40121

In conducting the research described in this manuscript the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of the Laboratory Animal Resources, National Academy of Sciences—National Research Council

The Relation Between Temporary Threshold Shift and Permanent Threshold Shift in Rhesus Monkeys Exposed to Impulse Noise

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Generalizing from later research these past failures were reasonable. Temporary threshold shift from any particular noise exposure cannot be used as an index of an ear's general susceptibility to fatigue (Ward, 1971). For example an ear's susceptibility to TTS from low frequency noise does not adequately predict its susceptibility to high frequency noise (Ward, 1968) and its susceptibility to noise at one intensity may not predict its susceptibility at a higher intensity (Kryter 1970 p 168). At best, TTS could only be used to pick out the most susceptible individuals within a given noise environment (e.g. Pfander 1968 1969). Even this relationship has not been firmly established. Thus more studies are needed.

As a test of the correlation between *initial* susceptibility to TTS and later susceptibility to PTS from a single noise source 10 rhesus monkeys were given behavioral audiograms and exposed repeatedly to impulse noise. After each exposure subjects were tested until recovery from TTS was complete. Permanent *threshold shift* was measured 64 days after the last exposure.

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Experimental Psychology Division, US Army Medical Research Laboratory Fort Knox, Kentucky 40121 USA

[2] Present Address: Department of Psychology Memphis State University Memphis, Tennessee 38111

[3] ENT Clinic Ireland Army Hospital, Fort Knox, Kentucky 40121

[4] In conducting the research described in this manuscript, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of the Laboratory Animal Resources National Academy of Sciences—National Research Council

end of the 3 sec stimulus The shock was terminated only when the animal was completely across the barrier

On the day after animals avoided the shock for 18 out of 20 trials generalization training was initiated Gradually the animals were exposed to the higher and lower frequencies to be used in threshold testing

Pre-threshold training was begun when the animals avoided the shock twice successively at each test frequency At this point attenuation of the test tones was begun usually in 10 or 20 dB steps, depending upon the animal This stage of training continued until the animals were thoroughly accustomed to changes in both intensity and order of presentation of the frequencies

Threshold procedures

Although the procedure for obtaining thresholds varied somewhat according to the stage of the experiment the basic procedure was merely a refined continuation of pre-threshold training The tone was attenuated in steps of 20 dB until the animal failed to respond then was increased by 10 dB and then further increased or decreased by 5 dB according to whether the animal responded to the increase of 10 dB His final score (in dB) for that frequency was halfway between the least intensity eliciting a response and the next lowest intensity

In obtaining any threshold it was necessary for the experimenter to be reasonably certain that the animal was attending to the signal Early in training most of the animals began orienting their intact ear toward the speaker It was assumed that this position indicated attention by the animal and care was taken to initiate the more difficult trials when the animal was in this position Shock was usually omitted on difficult trials

A modified procedure was used in evaluating temporary threshold shift. Immediately after an impulse exposure the monkey was transferred to the shuttlebox Since 1 to 3 min were required for a threshold determination, only one frequency could be studied during the first 10 min after an exposure The frequency chosen was 2 000 Hz. After the first 10 min TTS was evaluated at the additional frequencies of 1 8 and 14 kHz and thresholds were determined periodically until recovery was complete at all four frequencies During the first hour after exposure testing was carried on continuously A stopwatch was used to record the exact minute at which a determination was made For this reason the test periods were distributed randomly during the first hour Thereafter thresholds were determined at 2 4 8 hr etc until recovery to within 5 dB of preexposure threshold After continuous noise exposure only the 2 kHz threshold was tested

Schedule and sources of noise exposures

Monkeys were exposed to both continuous and impulsive noise The continuous noise used was originally recorded on an Ampex 600 tape recorder from inside an M60 main battle tank traveling on a hard surface road at 25 mph For the actual exposure a tape loop of this noise was played back amplified and fed to an Altec 515 low frequency speaker The speaker was in one corner of the anechoic chamber The sound level at 15 in. from the cone of the speaker (the level of the monkey's ear during exposure) was 110 dB as measured on the linear scale of the Bruel and Kjaer Type 2112 Audio Frequency Spectrometer A one third octave band analysis of this noise revealed a peak at 500 Hz with a negative slope of 10 dB per octave between 500 Hz and 12 000 Hz. For a graph of the analysis see Fig. 1 of Luz Fletcher Fravel & Mosko (1971)

The impulse noise was generated with a multiple spark-gap generator devised by R. W Benson and Associates The 4-gap condition was used (cf Loeb & Fletcher 1968) This condition yielded a pulse with a condensation of 168 dB and 60 μsec duration and a rarefaction of 165 dB and 100 msec dura-

others the five males (M 2 M 3 M-4 M 64 and M 25) ranged from four to eight years of age and the females (M 30 M 39 M-43 M-47 and M-49) from three to five years of age (cf Luz Fletcher Mosko & Fravel 1971 *for further details*)

The surgery was *performed in the USAMRL* surgical suite by Dr William Fravel a qualified ENT surgeon on the staff of the post military hospital

With the monkey under general anesthesia the right middle ear was approached through a post-auricular incision The posterior bony canal wall was drilled away until access to the middle ear was attained All middle ear ossicles were removed to include the foot plate The vestibule was then entered with a large curved pick and the instrument was manipulated to destroy inner ear anatomy—the free flow of inner ear fluid was controlled by packing with sterile gel foam The tympanic membrane was destroyed along with the annulus The middle ear and external bony canal were packed with gel foam the incision closed and the animal placed on postoperative antibiotics

Apparatus

A two-way shuttlebox was used for the training and testing of the monkeys In its interior it was 81 cm long 36 cm wide and 63 cm high The dividing barrier was 23 cm The sides and top were made of steel bars sunk into a sheet metal base A sheet metal pan resting on the base was filled with a 4 inch layer of San i-Cel In addition to absorbing the droppings this material damped reflections from the base of the shuttlebox Shock to the shuttlebox was under manual control and could be applied in the following combinations left side right side left plus barrier right plus barrier barrier alone

During testing the subject was observed on a closed circuit TV Although two flood lights were needed for an adequate picture the level of illumination in the test chamber was generally low

Acoustic environment and calibration of the audiometer

The shuttlebox was placed in the center of a windowless anechoic chamber for the threshold testing Fiberglass wedges covered all six inside planes of the chamber An AR 3 speaker suspended 76 cm above the top of the shuttlebox was fed by a shielded cable which was passed through the wall of the chamber

The pure tones were generated by a Hewlett Packard oscillator gated by a Grason-Stadler vacuum tube switch and amplified by a Krohn Hite 50 watt power amplifier Transistor logic was used to control the electronic switch The signal consisted of three 0 5 sec pulses of 50 msec rise and decay time with a 0 5 sec off time At the end of 3 sec a signal light informed the experimenter that the trial had ended A Ballantine voltmeter was used to check the audiometer output voltage before each session and an Erie Frequency Counter was used to check the frequency of the stimulus before threshold determination

The resulting sound field was measured at 20 different positions within the shuttlebox A Bruel and Kjaer Audio Frequency Spectrometer (Type 2112) and 1/2 condensor microphone (4133) were used For the six audiometric frequencies used (1 2 4 8 10 and 14 kHz) the standard deviations of the SPl measures were 2 2 5 6 5 and 5 respectively The mean of these settings was used as an estimate of the sound field The audiometer system was measured at the maximum levels used for the monkeys (70–80 dB)

Training procedures

Animals with previous avoidance training required only minimal familiarization before beginning actual threshold determinations The following procedure was used with untrained animals

Twenty trials of avoidance conditioning to a 1 kHz pulsed tone at 75 dB SPL were given daily Random intervals between trials were 1 to 2 min The animals were shocked if they failed to cross the dividing barrier before the

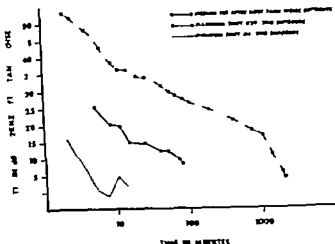


Fig. 1 Recovery from temporary threshold shift after exposure to 1 min of tape recorded tank noise. The median shift seen in nine monkeys after the first exposure to this noise (solid line) is compared with the largest shift (M-39 dashed lines) and the smallest shift (M-4 dotted lines) seen after the second exposure.

recent study of lemur hearing (Mitchell et al 1970) Three lemurs showed the dip three lemurs did not. Neither sex nor age nor species could account for the difference Other studies in which the 4 kHz dip did not occur are Semenoff & Young (1964) and Fujita & Elliott (1965)

Recovery afte exposure to tank noise

The 1? min exposure to the tape-recorded tank noise was relatively innocuous In fact the TTS was too transient to permit adequate test ing at more than one frequency The frequency chosen was 2 kHz.

It was impossible to obtain measures of TTS at exact, prearranged intervals of time However each subject s recovery was monitored carefully enough to allow adequate interpolations for statistical comparisons Such a comparison is given in Fig. 1 which contains a recovery function based on the median TTS of nine subjects (solid lines) Because of missing data the function is only defined between 5 and 80 min after exposure Over this range the recovery is a logarithmic function of time after exposure

The median statistic is an adequate reflection of individual data With one notable exception, all subjects showed a logarithmic recovery The one exception M-43 showed a "delayed recovery" a type previously described by Ward

Both the largest and the smallest individual records of TTS were seen after the second exposure to the noise These records are also shown in Fig. 1 The animal with the least TTS M-4 had shown the second to the largest amount of TTS_2 after his first exposure In contrast, M 39 who had shown the least TTS_2 after the first exposure had the most TTS_2 after the second exposure

Most of the subjects (seven out of nine) showed less TTS_2 after the second exposure than after the first. This drop in measured TTS was not the result of an increase in the pre-exposure threshold between the first and second exposure If anything sensitivity at 2 kHz had improved (mean thresholds of 7 dB and 3 dB SPL, respectively). The group correlation between TTS on the first and second exposures was negative (−0 74)

Recovery after exposure to the two-impulse condition

In the preceding section, the TTS following exposure to tank noise was shown to recover as a linear function of the logarithm of time. This relation was expected since it had been shown to occur for animals as diverse as man (Ward et al 1958) cat (Miller et al 1963) chinchilla (Peters 1965) rat, and monkey

Table I *Sequence of exposure conditions* (in days)

	Subjects									
Exposure	4	64	3	49	39	47		43	30	5
impulses	1	1	1	1	1	1	1	1	1	1
tank noise	28	8	9	4	30	17	1	14	14	
impulses	4	38	42	37	44	30	35	28	28	
impulses	53	55	56	51	58	44	46	42	4	
tank noise	73	83	70	63	66	57	60	51	58	
10 impulses	91	104	84	77	90	79	78	64	77	
20 impulses				11		98				

Schedule of exposure for each subject The order in which each monkey received his first impulse exposure (Day 1) is reproduced from left to right Vertical entries record the day after the first impulse exposure on which the monkey received each successive exposure Blank entries indicate that no exposure was given

tion (when measured with a Bruel and Kjaer model 4136 microphone feeding into a Tektronix storage oscilloscope) These measurements were made at 10 in from the spark gap the level of the monkey s ear during exposure (Measurements were made without the presence of the experimental animal) Compared with impulses from typical military (Kryter & Garinther 1966) or industrial sources (Martin Atherly & Hempstock 1970) this impulse was shorter with its energy spectrum peaked at higher frequencies

Monkeys were exposed with the left ear at normal incidence to the spark gaps Successive impulses were separated by 1 sec of silence Two impulses were used for the induction of TTS while 10 or 20 impulses were used for the induction of PTS

Since one purpose of this study was to establish a relation between TTS and PTS the least noxious exposures were made first There were five presented in the same order for each of nine subjects two impulses tank noise two impulses two impulses and tank noise A tenth subject a monkey with an obvious preexperimental hearing loss was terminated after the first exposure Preceding each of these exposures the threshold sensitivity of each monkey was reevaluated At the end of this schedule the nine subjects received an exposure of 10 successive impulses In addition two monkeys manifesting no PTS from the 10 impulses received another exposure to 20 successive impulses

Adequate time was given for recovery after every exposure Since this time varied slightly from subject to subject the exact day of exposure varied between subjects The exposure schedule for each is given in Table I Recovery from the maximal impulse noise exposure was measured at 1 2 4 8 16 and 32 days A final audiogram was determined for each subject following day 64

RESULTS

Pre-exposure audiogram

For the range of frequencies tested nine of the 11 monkeys were considered normal when compared with the results of Behar et al (1965) and Stebbins et al (1966) One abnormal animal M 25 had a striking high frequency loss (a 55 dB drop in threshold between 10 and 12 kHz) The other gave ambiguous results and was dropped Although his mean thresholds were initially similar to those of the other monkeys the variance of his thresholds was large and he finally stopped responding altogether (Later histology showed this animal to have hair cell damage of unknown origin) A graphic comparison of the mean thresholds for the nine normal subjects with previous published data from the same laboratory may be found in Fig. 2 of Luz Fletcher Fravel & Mosko (1971)

The group audiogram did not show a dip at 4 000 Hz In contrast most studies of primate hearing have found a dip of insensitivity at 4 000 Hz It was first noted in the chimpanzee (Elder 1934) It was also found by Wendt (1934) Harris (1943) Behar et al (1965) and Stebbins et al (1966) In addition it appears in the cochlear microphonic of rhesus monkeys (Vernon 1967) Thus it is surprising that it did not appear in the present series of monkeys This failure to find the 4 kHz dip is parallel to the results of a

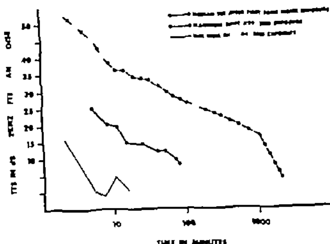


Fig. 1. Recovery from temporary threshold shift after exposure to 12 min of tape recorded tank noise. The median shift seen in nine monkeys after the first exposure to this noise (solid line) is compared with the largest shift (M 39, dashed lines) and the smallest shift (M-4, dotted lines) seen after the second exposure.

recent study of lemur hearing (Mitchell et al 1970). Three lemurs showed the dip; three lemurs did not. Neither sex nor age nor species could account for the difference. Other studies in which the 4 kHz dip did not occur are Semenoff & Young (1964) and Fujita & Elliott (1965).

Recovery after exposure to tank noise

The 12 min exposure to the tape recorded tank noise was relatively innocuous. In fact, the TTS was too transient to permit adequate testing at more than one frequency. The frequency chosen was 2 kHz.

It was impossible to obtain measures of TTS at exact prearranged intervals of time. However, each subject's recovery was monitored carefully enough to allow adequate interpolations for statistical comparisons. Such a comparison is given in Fig. 1, which contains a recovery funcion based on the median TTS of nine subjects (solid lines). Because of missing data, the function is only defined between 5 and 80 min after exposure. Over this range, the recovery is a logarithmic function of time after exposure.

The median statistic is an adequate reflection of individual data. With one notable exception, all subjects showed a logarithmic recovery. The one exception, M-43, showed a delayed recovery, a type previously described by Ward.

Both the largest and the smallest individual records of TTS were seen after the second exposure to the noise. These records are also shown in Fig. 1. The animal with the least TTS, M-4, had shown the second to the largest amount of TTS after his first exposure. In contrast, M 39, who had shown the least TTS_2 after the first exposure, had the most TTS after the second exposure.

Most of the subjects (seven out of nine) showed less TTS_2 after the second exposure than after the first. This drop in measured TTS was not the result of an increase in the pre-exposure threshold between the first and second exposure. If anything, sensitivity at 2 kHz had improved (mean thresholds of 7 dB and 3 dB SPL, respectively). The group correlation between TTS on the first and second exposures was negative (−0.74).

Recovery after exposure to the two-impulse condition

In the preceding section, the TTS following exposure to tank noise was shown to recover as a linear function of the logarithm of time. This relation was expected, since it had been shown to occur for animals as diverse as man (Ward et al. 1958), cat (Miller et al. 1963), chinchilla (Peters, 1965), rat, and monkey

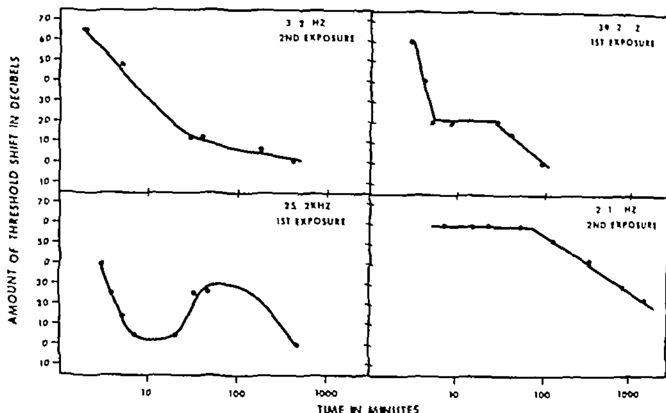


Fig. 2. Curves of recovery from TTS seen in the rhesus monkey after exposure to impulse noise. A logarithmic recovery was shown at kHz for M 3 after the second impulse exposure. A rebound recovery was shown at kHz by M 5 after her only impulse exposure. A diphasic recovery was shown at kHz by M 39 after the first impulse exposure. A delayed recovery was shown by M at 14 kHz after his second impulse exposure. Other examples from different subjects in the same experiment may be found in Luz and Hodge (1971).

(Harris 1967). A log-linear function was also expected to follow the monkey's exposure to impulse noise and it did. In addition several other types of recovery were noted.

These non logarithmic functions (rebound diphasic recovery and plateau) have also been found in humans exposed to high levels of gunfire (Luz & Hodge 1971). Schematic examples of the four types of recovery functions may be found in that report. Actual examples taken from the subjects of the present study are shown in Fig. 2. Additional records from these same monkeys may also be found in Luz & Hodge.

The presence of these different types of recovery functions is also reflected in the group statistics. In Fig. 3 median values of TTS are given over the intervals of 5 to 480 min of 2 kHz and 15 to 480 min for 8 and 14 kHz. Although the median values followed a logarithmic recovery at 2 kHz they reflected a rebound recovery at the higher frequencies of 8 and 14 kHz. Because one subject showed evidence of PTS after the first exposure to impulse noise only the values from the first exposure were used in Fig. 3.

After each impulse noise exposure a subject was allowed a recovery period of about four weeks. Two subjects did not recover to within 10 dB of their pre-exposure thresholds during this period. The TTS remaining at that time was called PTS. Subject M 2 suffered a PTS at 14 kHz of 15 dB after the first impulse exposure and M-4 suffered a PTS of 35 dB at 8 kHz after the second impulse exposure. Some of the other subjects suffered insignificant amounts of PTS in the order of 5 to 10 dB. At the end of five TTS exposures the mean loss for the nine subjects was 0 dB 3 dB 4 dB and 9 dB at 1 2 8 and 14 kHz respectively.

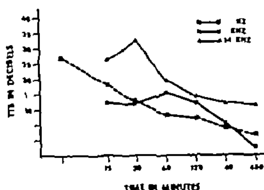


Fig. 3. Median values of TTS for nine monkeys after the first exposure to tw impulses. Values are defined at 2 kHz beginning at 5 min. For 8 and 14 kHz, values begin at 15 min. For the frequency showing the most enduring TTS 14 kHz, only two monkeys had not recovered to within 10 dB of pre-exposure threshold at 16 hr after the exposure.

Threshold shift after ten and twenty impulse conditions

Following the recovery period for the last exposure to tank noise all monkeys were exposed to ten successive impulses. The amount of threshold shift was determined for 1 2 4 8 10 and 14 kHz at 24 hr 2, 4 8 16 and 3 days following exposure. The two most resistant monkeys M-47 and M-49 recovered within a few days of the exposure and were subsequently exposed to 20 additional impulses.

The course of recovery at the six test frequencies is shown in Fig. 4 which is based on the median values of threshold shift found after the maximum exposure for each monkey. The reference thresholds zero shift are the thresholds determined immediately before the exposure to the ten impulse conditions.

The median threshold shift was greatest at 8 or 10 kHz during the first eight days at 10 or 14 kHz for the next 4 days and at 14 kHz at the sixty-fourth day. This change in the maximum threshold shift may also be seen in Fig. 5 which shows the amount of shift as a function of frequency for each of the seven test days.

The rapid drop in median shift at 8 kHz between eight and 16 days was mainly due to one animal M-64. His recovery at 8 kHz was a linear rather than a logarithmic function of days after exposure. Although this linear recovery was not common it did occur in other animals. Examples for M-49 at 1 kHz, M 3 at 4 kHz M-64 at 8 kHz and M-47 at 14 kHz are given in Fig. 6. There also appeared to be some hybrid recovery functions recoveries that were linear in time and then logarithmic in time.

At the end of 64 days the final audiogram was determined for each subject. An audio-

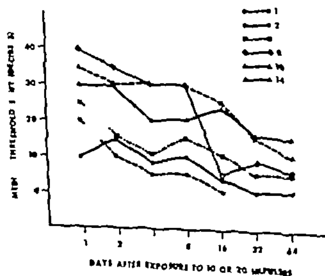


Fig. 4. Median amount of threshold shift found at 1 2, 4 8 16, 32, and 64 days after the maximum exposure to impulse noise received by each of the nine monkeys. The reference thresholds (0 dB) are those found immediately before the exposure to the 10 or 20 impulses.

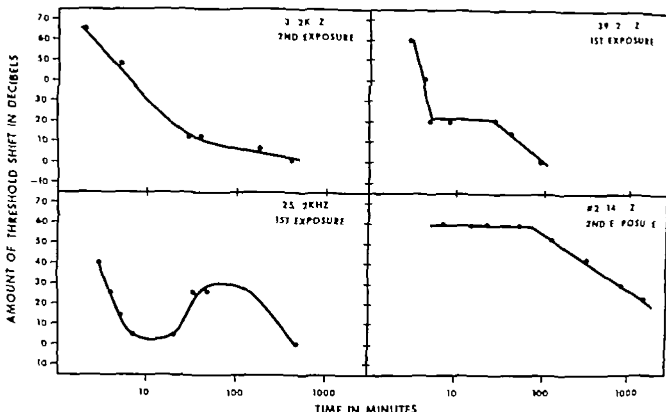


Fig 2 Curves of recovery from TTS seen in the rhesus monkey *after exposure to impulse noise A logarithmic* recovery was shown at kHz for M 3 after the second impulse exposure A rebound recovery was shown at 2 kHz by M 25 after her only impulse exposure A diphasic recovery was shown at kHz by M-39 after *the first impulse exposure A delayed recovery was shown* by M 2 at 14 kHz after his second impulse exposure Other examples from different subjects in the same experiment may be found in Luz and Hodge (1971)

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TTS recovery vs PTS profiles of TTS vs profiles of PTS etc. No meaningful relations could be established

DISCUSSION

No significant correlation was found between the TTS produced from an initial exposure to two impulses and the PTS seen at 64 days after exposure to ten impulses. For example M-49 and M 39 showed an average TTS of 15 dB and 14 dB respectively for ? 8 and 14 kHz at 30 min after initial exposure. However M-49 suffered the least PTS of any monkey while M 39 suffered the largest dip in its audiogram. The final audiogram of M 39 was most similar to that of M-4 the monkey with the largest amount of TTS after the initial exposure

Although a large amount of TTS did not predict a large amount of PTS *it did* predict the early development of PTS Only two animals (M 2 M-4) showed a TTS_{30} as great as 50 dB (at any frequency) after the first exposure These same two animals were the only ones to show a PTS as much as 20 dB (at any frequency) after recovery from the second exposure. Following the third impulse exposure a third monkey showed a loss of 20 dB and following the 10 impulse exposure six of the nine normal monkeys showed a PTS of as much as 20 dB at any frequency

Other significant correlations were either trivial or unexpected The correlations between TTS at different frequencies (Table II) were comparable to those found for humans exposed to the same impulse noise source (Fletcher & Loeb 1965) The negative correlation (p (0 05) seen after the first and second exposure to tank noise was unexpected Evidently the characteristics of these ears were being changed during the process of repeated exposures Also unexpected was the association of non-logarithmic recovery patterns with impulse noise exposure. These nonlogarithmic recovery patterns appeared to be qualitatively related to susceptibility This was

Table II *Intercorrelations between the amount of TTS seen in each subject at 30 min after the first impulse exposure at the test frequencies of 1 2 8 and 14 kHz and the mean amount of PTS at 8 10 and 14 kHz seen in that subject after the maximal exposure a e given above the d'agonal*

Analogous correlations for TTS at 120 min are given below the diagonal (For two-tailed test and seven degrees of freedom, **means significanc at the 0 01 probability level and t the 0 02 level)

	30				
120	1 kHz	2 kHz	8 kHz	14 kHz	PTS
1 kHz		.88**	.87	60	.01
2 kHz	95**		.85	48	11
8 kHz	96	95**		.83	– 14
14 kHz	75	78	.88		– .33
PTS	64	11	01	– 15	

a weak relationship and was most apparent following recovery from the third impulse exposure At that time each of the three monkeys showing 20 dB PTS at any frequency had also shown a rebound at 2 kHz after each of the three -impulse exposures For those six monkeys showing less PTS a rebound was detected at 2 kHz in only five of 17 recovery records

The rhesus monkey appears to be more susceptible than man to impulse noise The comparative data may be found in past reports from this laboratory (Fletcher & Loeb 1965 Fletcher & Loeb 1967 Fletcher 1969) These reports describe the levels of TTS sustained by dozens of volunteers who were exposed to the same impulse source as used in the present study In one study (Loeb & Fletcher 1968) the median subject required over 20 of these impulses to reach a TTS_2 of 30 dB at any frequency None of the human subjects have failed to recover from exposure to these impulses

The monkeys were also more susceptible to the continuous noise than human subjects, having been exposed to the same tank noise as were some volunteers from a concurrent study The young men demonstrated a median

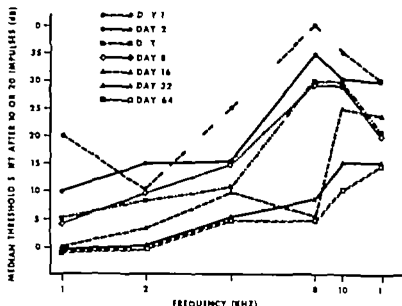


Fig 5 Median amount of threshold shift as a function of frequency after the maximum exposure to impulse noise received by each of the nine monkeys. As in Fig. 4 the reference thresholds are those taken immediately before each monkey's exposure to 10 impulses. Profiles are given for days 1 ... 4 8 16 3 and 64 for the frequencies of 1 ... 4 8 10 and 14 kHz.

gram was also determined for M 25 the subject that had pre-exposure high frequency hearing loss *The most resistant subjects were* M-47 and M-49 each of which received twenty impulses The audiograms of M-43 and M-64 were close to normal but showed *an abrupt loss at 14 kHz. Still* more severe high frequency loss was found for M 30 and M 2 Although their loss at 14 kHz was comparable M 2 had much more loss in the lower frequencies The most severe high frequency loss was found for M 25 and M 3 Finally two animals showed a clearly defined audiometric dip M-4 and M 39 The dip was broadest for M 39 Comparisons between these and the pre-exposure audiograms may be found in Figs 24 25 28 30 and 31 The actual audiograms may be found in Fig 12 through 16 of Luz, Fletcher Fravel & Mosko (1971)

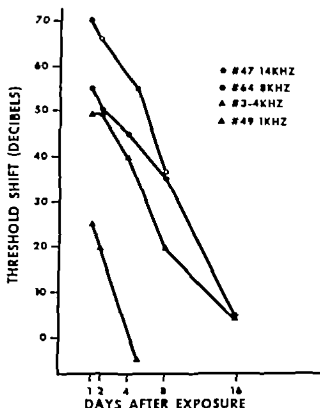


Fig 6 Rapid recoveries seen at some test frequencies after exposure to 10 or 20 impulses Although most threshold shifts recovered as a linear function of the logarithm of days of recovery these shifts recovered as a linear function of the number of days of recovery

As an index of the amount of PTS the PTS at 8 10 and 14 kHz was averaged for each subject This figure was then correlated with the TTS at 1 2 8 and 14 kHz at 30 and 120 min after the first exposure to the two-impulse condition (Table II) The correlations between the amount of TTS for different frequencies were remarkably large but the correlations between the measures of TTS and PTS were remarkably non-existent Although the correlations between TTS at the different test frequencies improved between 30 and 120 min the TTS-PTS correlations remained close to zero Several other correlations were attempted averaged TTS vs PTS slope of

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	30				
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PTS	04	– 11	01	15	

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The monkeys were also more susceptible to the continuous noise than human subjects, having been exposed to the same tank noise as were some volunteers from a concurrent study The young men demonstrated a median

TTS of 26 dB for 2 kHz at 90 sec after exposure. This figure is almost equal to the median shift at 2 kHz found among the monkeys at 5 min after the equivalent exposure.

Another difference in susceptibility between monkey and human was observed in this study—a *difference in patterns of PTS*. When human hearing is damaged by impulse noise, three classes of pure tone audiograms are found: dips (typically at 4 kHz), divided dips, and abrupt high frequency losses (Salmivalli 1967). In Salmivalli's study of acoustic trauma among Finnish soldiers, 75% showed a dip, 11% a divided dip, and 14% an abrupt loss. In the present study, only two of the nine monkeys showed a well defined dip (M-4 and M-39). For the other seven, the loss was maximal at the highest frequency tested, 14 kHz. (Two of these seven, M-34 and M-47, appeared to have a "divided dip" but the evidence is equivocal on this point.) Too little is known of the anatomy of the monkey ear to permit an interpretation of these *differences between man and monkey*. However, it is tempting to relate these differences to the differences between the minimum *audible fields of man and rhesus*. *The rhesus* is less sensitive than man below 4 kHz but is sensitive to frequencies at an octave above man's upper limit (Behar, Cronholm & Loeb, 1965).

Two unexpected changes occurred in the sensitivity at 1 and 2 kHz. First, there was an apparent increase in sensitivity at these frequencies after the loss of higher frequency hearing. Second, there was a decrease in susceptibility to TTS at these frequencies.

The increase in sensitivity at 1 kHz was found in seven of the nine monkeys. It was also found in the abnormal subject, M-25. Only three of the monkeys showed an improvement at 2 kHz (M-4, M-2, and M-49). Such an increase of sensitivity to low frequency tones is thought to follow destruction of more basal hair cells and has been ascribed to a decrease in the lateral inhibition exerted by one set of neurons on another set (Carterette 1969). Since Carterette has cited *many* examples of this phenomenon, it seems reasonable that a real change in sensitivity could *have occurred in the present study*. *However*, the evidence should be interpreted with caution, since there was no control group in the experimental design.

During the course of the three "2-impulse" exposures and the two tank noise exposures, a resistance to TTS appeared in the low frequencies, 1 and 2 kHz. This resistance was demonstrated in two ways: (i) By comparison of the highest absolute thresholds observed at 20 or more minutes after the first and third exposure to the "2 impulse" condition. (ii) By comparison of TTS_4 at 2 kHz after the first and second exposure to tank noise. Out of nine monkeys, eight showed less absolute shift at 1 kHz after the third "2-impulse" exposure than after the first. At 2 kHz, five out of nine showed less shift. In contrast, at 8 and 14 kHz, six out of nine showed *more* absolute shift between these two exposures. An *increased tolerance to low frequency* noise was demonstrated when seven out of nine monkeys showed less TTS_3 after *their second exposure to tank noise than after* their first. This increased tolerance cannot be attributed to a decrease in sensitivity at 2 kHz, for, *if anything, sensitivity had increased at* this frequency.

A similar increase in resistance to noise was reported for the rhesus and impulse noise by Romba & Gates (1964) and for cats and continuous noise by Miller et al. (1963). In addition, there are at least four reports in which decreases in TTS occurred for humans (Murray & Reid, 1946; Coles, 1962; Loeb & Fletcher, 1963; Ward, 1970). Each of these reports involved hazardous exposures—impulses (Murray and Reid; Coles) and high intensity intermittent noise (Loeb & Fletcher; Ward). The noises used in all four studies have four features in common: (i) They produce high levels of TTS. (ii) They sometimes produce aberrant (non-logarithmic) recovery functions. (iii) The variance *in TTS between*

subjects is typically greater than for continuous noise (iv) They often produce a phase of supranormal excitability" (Murray & Reid 1946) at some test frequencies (Ward 1970; Hodge & McCommons 1966) Although increased resistance to noise is not invariably found after this type of exposure it may occur often enough to account for the popular belief in toughening ears a superstition shared by many workers in high noise environments

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Cochlear Pathology in Monkeys Exposed to Impulse Noise

by Valdemar M Jordan [1] Marilyn L Pinheiro [1] Kazuo Chiba [1] and Armando Jimenez[1]

INTRODUCTION

Many humans both in military and civilian life are subject to exposure to the intense pressure waves of impulse noise Early reports on cochlear damage due to this type of acoustic trauma were made by Hamberger & Hyden (1945) on guinea pigs by Perlman (1948) on rabbits and by Lindquist Neff & Schuknecht (1954) on cats These investigators used decalcification and serial sectioning to prepare their specimens Recently improved methods of histological preparations have made it possible to carry out more accurate and detailed evaluations of cochlear structure

By using the surface preparation technique histologists have been able to compare the patterns of hair cell damage induced by differently shaped impulses Poche Stockwell & Ades (1969) used the surface preparation technique to explore hair cell destruction in guinea pigs after exposure to cap gun fire Also in the guinea pig Hamernik Henderson Dosanjh & Sitler (1971) studied the effects of impulses generated by a shock tube and by an exploding wire Together with the sonic boom study of Majeau-Chargois Berlin & Whitehouse (1967) these studies form a valuable intraspecies comparison

A different approach to the study of impulse noise is the interspecies comparison the approach of the present study Rhesus monkeys were deafened by exposure to a spark gap impulse This impulse had been previously used in several studies with humans (Loeb & Fletcher 1968 Fletcher 1969 Fletcher & Loeb 1965 Fletcher & Loeb 1967) and in one study with chinchillas (Luz & Mosko 1971)

METHOD

Subjects

The left ears of ten rhesus macaque monkeys had been exposed to impulses (The one abnormal subject M 25 omitted from most analyses in the previous report was included) Total exposures ranged from two impulses for M 25 through 16 impulses for M ? M-4 M 30 M 39 M-40 and M-64 and to 36 impulses for M-47 and M-49 These figures represent multiple exposures ranging up to four months Subjects were studied at least three months after the last exposure

Preparation

In order to avoid confusion between post mortem changes (Jordan et al) and pathological lesions the monkey ears were fixed in vivo using general anesthesia and the principles of mastoid surgery The animals were anesthetized by intramuscular injection of serylan (0 5–1 0 mg/kg of body weight) and by subcutaneous atropine sulfate (0 0? mg/lb of body weight) The left ear was prepared and draped in the usual surgical manner The overlying soft tissue was rapidly removed by sharp and blunt dissection Under the dissecting microscope cutting burrs were used to

[1] Case Western Reserve University Medical School Cleveland Ohio 44106 USA

In conducting the research described in this report the investigators adhered to the Guide for Laboratory Animal Facilities and Care as promulgated by the Committee on the Guide for Laboratory Animal Resources National Academy of Sciences—National Research Council

penetrate the cortex at Henle's spine. The mastoid antrum was located first and then a simple mastoid cavity was created The posterior canal wall and the lateral wall of the atti were removed to provide good exposure of the tympanic membrane By sharp dissection with suitable elevators the ear drum was lifted out of the annulus to expose the incudostapedial joint This was carefully separated so that as the drum was turned forward, it carried the attached malleus and incus with it. In this manner excellent visualization of the medial wall of the middle ear was obtained All essential structures could be identified easily

Actual fixation of the inner ear was carried out in the following manner The round window membrane was carefully punctured by a microscopic right-angle pick Next, the stapes with its footplate was extracted from the oval window Then micropipettes were used to perfuse the fixative solution (paraformaldehyde containing 0 5% glutaraldehyde with a pH of 7 4) through the round window opening into the scala tympani Gentle perfusion was continued until the fixative could be seen welling out of the oval window This procedure was repeated over a fi e minute period to be certain that as much perilymph as possible had been replaced by the fixative Finally each window was sealed with dental wax

The dorsum of the skull was then exposed A central opening in the bone was made with a Stryker temporal bone saw This was rapidly enlarged with rongeurs until it was possible to enucleate the brain sacrificing the animal The left temporal bone was immediately removed using the Stryker saw in the manner reported by Schuknecht (1968) The bone plug was reinfused at once with the paraformaldehyde according to the method described above The windows were left open, and the specimen was immersed in the fixative for a minimum of twenty-four hours The inner ears were later stained with buffered osmic acid solution (0.5%) using the same procedure as for fixation. The stain was left sealed in the perilymphatic spaces for 30 min The cochlea was then flushed thoroughly with 70% ethanol in which it was immersed until cochlear dissection could be performed

Dissection

Microdissection and surface preparations were used to study the 10 monkey cochleae This method originally used by Retzius (1882 1884) was revived and revised by Engstrom Ades & Hawkins (1964) who have adequately described the procedures followed in this investigation Through the use of this method individual hair cells could be counted and percentages of losses accurately plotted against the distance from the basal end of the basilar membrane. The nerve fibers could be easily observed. Thus complete histological data could be made available for comparison with the clinical findings on the experimental animals

Before beginning exposure of the cochlea each window was resealed with dental wax to prevent the scalae from being contaminated with bone dust. Under the Zeiss binocular microscope and a 70% alcohol drop the labyrinthine bone was rapidly removed with a high speed dental drill As the overlying bone was thinned the membranous inner ear was easily recognized because of the dark osmic acid stain. Thus the contour of the cochlea and the semicircular canals could be followed in the drilling. Correct shaping of the bony cochlear coils was essential in order to facilitate the later removal of the basilar membrane and its superstructure When the bony labyrinthine covering had been made eggshell thin the specimen was again immersed in 70% ethanol and examined under the stereomicroscope Special dental picks were used to flick away carefully the thinned soft residual bony shell uncapping the cochlea. After removing the spiral ligament the stria vascularis, Reissner's membrane and the tectorial membrane the entire length of the cochlea from cecum ves-

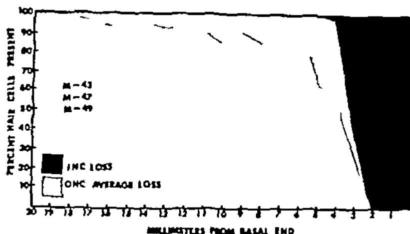


Fig 7 Group I Averaged hair cell loss for M-43 M-47 and M-49 Outer hair cell loss overlaps all inner hair cell loss

tibulare (hook) to helicotrema could be observed Under low power magnification it was possible to estimate the extent and location of damage to the organ of Corti and myelinated nerve fiber bundles Phase contrast microscopy was used for studying the finer deails of cytoarchitecture

The length of the basilar membrane from its basal end in the hook area to its apical termination was carefully measured along the inner hair cells by means of a calibrated optical scale under 400X magnification. The basilar membranes of the 10 monkeys ranged in length from 23 30 mm to 25 80 mm with a mean length of 24 59 mm

Both inner and outer hair cells were counted in each cochlea Their exact locations were plotted on cochleograms A sensory cell was considered present if it could be observed even though it might appear abnormal in some way—i e pulled away from pillar cells swollen or with stereocilia absent Single or small groups of missing hair cells were counted by the phalangeal scars which replaced them The number of hair cells missing in a destroyed segment could be estimated from the average number of hair cells in normal adjacent segments of the same length Some fourth row outer hair cells were observed but these were not documented because there was no regularity to their presence The percentage of hair cells in each row was calculated from the cochleograms for every half millimeter along the basilar membrane These percentages were used to plot graphs of the damage

RESULTS

The most obvious result of this study was the great variability in extent and severity of cochlear damage The cochleae studied seemed to fall into three distinct groups

Group I (M-43 M-47 and M-49) showed the least damage (Fig 7 also Fig 23) Each had an area of destruction along the initial two to three millimeters of the basilar membrane in the hook area. Here both the myelinated nerve fibers and the organ of Corti had been totally destroyed Some thin flat epithelial cells were observed paving the basilar membrane Beyond this damaged area myelinated radial nerve fiber bundles crossing the osseus spiral lamina appeared abruptly (Fig. 8) In M-43 and M-47 the nerve fibers remained dense throughout the length of the cochlear coils In M-49 normal nerve fiber density was interrupted twice in the basal turn by narrow wedges of missing fibers (Fig. 9) The organ of Corti opposite these missing fibers was normal

The structure of the organ of Corti itself took shape on the basilar membrane opposite the beginning of the appearance of the nerve fibers Inner hair cells were observed first and reached a full complement within less than a millimeter Throughout the remainder of the

Fig. 8. M-43. Abrupt beginning of myelinated nerve fibers and organ of Corti (100)

Fig. 9. M-49. Missing wedge of myelinated nerve fibers (arrows) opposite normal organ of Corti (x100)

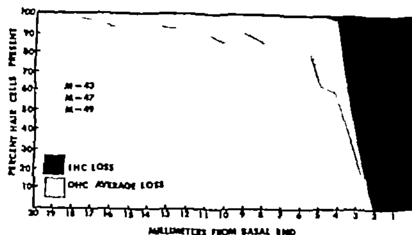


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Fig. 11. M-25. Extensive destruction ... hook area and lower basal turn. Note abrupt beginning of myelinated nerv... fibers followed by appearance of organ of Corti (×12).

tion of cochlear damage with variations only in degree of severity and extent along the basilar membrane. Hook area damage was limited to two to three millimeters of depleted myelinated nerve fibers and organ of Corti destruction. As soon as the darkly stained nerve bundles became dense, the cytoarchitecture of the organ of Corti was rapidly reorganized. Inner hair cells appeared first and outer hair cells followed closely. At about 4.0 mm from the basal end of these cochleae the population of sensory cells had reached near-normal percentages. Myelinated radial nerve fiber bundles showed normal density. In M-4, M-30, M-39 and M-64 a longitudinal separation between Hensen's cells and Deiters' cells was observed to extend for several millimeters along the lower half of the basal turn (Fig. 12). At 5.0 mm to 6.0 mm from the basal end, a precipitous outer hair cell loss occurred. The peak of this damage was located at 8.0 mm to 9.0 mm along the basilar membrane. In both M-4 and M-64 two narrow wedges of missing radial nerve fibers paralleled areas of complete disruption of the organ of Corti (Figs. 13 and 14). A slight loss of inner hair cells accompanied severe outer hair cell loss at 6.0 mm to 7.0 mm from the basal end in M-39 and M-64. M-4 had a more extensive inner hair cell loss in the region from 9.0 mm to 12.0 mm along the basilar membrane. These inner hair cell losses occurred only in areas where the organ of Corti itself was totally disrupted. Inner hair cells were usually present where the structure was partially intact. In some areas, where outer hair

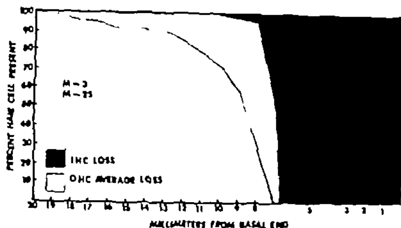


Fig 10 Group II Averaged hair cell loss for M 3 and M 25 Outer hair cell loss overlaps all inner hair cell loss

cochlea the inner hair cells were normal in *all three animals in this group* *Outer hair* cells appeared soon after inner hair cells with the innermost row I observed first followed by rows 2 and 3 All three rows rapidly increased to a near normal population In M-43 and M-47 there were two areas of outer hair cell loss further along the basilar membranes *Both animals had outer hair cells missing* at 8 0 mm to 9 0 mm from the basal end These losses were more marked for the third outer most row Rows 1 and 2 had only slight losses in the same regions *M-43 had a second wedge* of absent outer hair cells at 10 0 mm to 11 0 mm *M-47 had a* peak of third row outer hair cell loss *at 15 0 mm to 16 0 mm with the* damage to the row extending further basal ward than toward the apex M-49 was the cochlea most resistant to the noise trauma It was found to be different from the other cochleae—i e the first row of outer hair cells *showed the greater damage throughout the lower half of the basal turn* with a peak of 15% loss at 8 0 to 9 0 mm *In the upper* half of the basal turn the third row had more phalangeal scars indicating small regions of missing cells

In Group I only M-47 was observed to have a longitudinal split between Hensen s cells and Deiters cells in the lower section of the basal coil

Group II (M 3 and M 25) had the greatest *extent of complete* destruction of organ of Corti and myelinated nerve fibers in the hook area and lower portion of the basal turn In *both cochleae this* damage extended along the basilar membrane for about seven millimeters (Figs 10 26) *At this point the myelinated* radial nerve fiber bundles appeared abruptly and the structure of the organ of Corti took shape (Fig 11) Inner hair cells appeared suddenly In M 25 these increased to a full complement within a half millimeter In M 3 90% of inner hair cells were present in a half *millimeter with only occasional cells missing* along the next few millimeters of the basilar membrane

In both M 3 and M 25 the outer hair cells appeared shortly after the inner hair cells *These increased gradually throughout the ba*sal turn reaching a normal population in the lower half of the middle coil The outermost row of sensory cells was observed to be most damaged while the innermost row was least damaged Row 2 was only slightly more in*volved than row 1 and much* less so than row 3 Row 3 in both animals showed at least two areas *where the gradual increase in the* outer hair cell population was briefly reversed These foci of greater third row hair cell loss were marked by scarring of the reticular la*mina* Losses *peaked at 11 5 mm and 13 0* mm in M 3 and at 14 0 mm and 16 0 mm in M 25 Beyond 18 0 mm from the basal end these cochleae were normal in appearance

Group III included half the inner ears in this study M 2 M-4 *M 30 M 39 and M-64* demonstrated basically the same configura

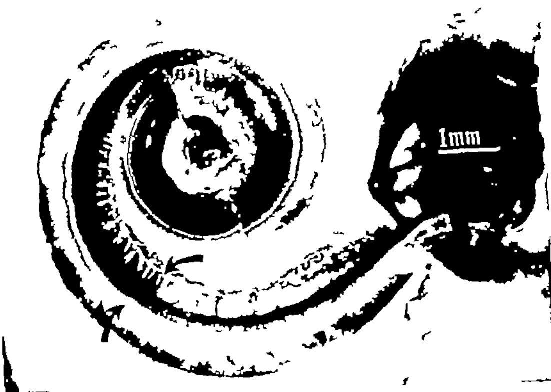


Fig. 11. M 25. Extensive destruction in hook area and lower basal turn. Note abrupt beginning of myelinated nerve fibers followed by appearance of organ of Corti (× 12).

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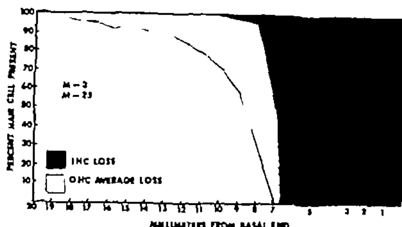


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Group II (M 3 and M 25) had the greatest extent of complete destruction of organ of Corti and myelinated nerve fibers in the hook area and lower portion of the basal turn In both cochleae this damage extended along the basilar membrane for about seven millimeters (Figs 10 26) At this point the myelinated radial nerve fiber bundles appeared abruptly and the structure of the organ of Corti took shape (Fig 11) Inner hair cells appeared suddenly In M 25 these increased to a full complement within a half millimeter In M 3 90% of inner hair cells were present in a half millimeter with only occasional cells missing along the next few millimeters of the basilar membrane

In both M 3 and M 25 the outer hair cells appeared shortly after the inner hair cells These increased gradually throughout the basal turn reaching a normal population in the lower half of the middle coil The outermost row of sensory cells was observed to be most damaged while the innermost row was least damaged Row 2 was only slightly more involved than row 1 and much less so than row 3 Row 3 in both animals showed at least two areas where the gradual increase in the outer hair cell population was briefly reversed These foci of greater third row hair cell loss were marked by scarring of the reticular lamina Losses peaked at 11 5 mm and 13 0 mm in M 3 and at 14 0 mm and 16 0 mm in M 25 Beyond 18 0 mm from the basal end these cochleae were normal in appearance

Group III included half the inner ears in this study M 2 M-4 M 30 M 39 and M-64 demonstrated basically the same configura



Fig. 14. M-4. Close-up of missing wedge of myelinated radial nerve fibers opposite disrupted organ of Corti (×200). NF = missing nerve fibers, OC = missing organ of Corti.

cells were entirely absent, the reticular lamina remained. Except for the missing wedges of nerve fibers described above, myelinated radial nerve bundles appeared normal throughout the cochleae beyond the hook area.

Beyond 10.0 mm along the basilar membrane, these inner ears showed a gradual restoration of outer hair cell population. Almost all outer hair cells were present in the apical half of the middle coil. Occasional degenerated cells were replaced by phalangeal scars on the reticular lamina. Scars were formed where outer hair cells were destroyed. The phalangeal processes of the supporting cells grew together at the reticular lamina to maintain its contiguity.

Group III could be subdivided according to severity and extent of hair cell destruction. M-4 and M 39 were the most severely damaged ears in this group with the greater portion of the basal turn of both cochleae disrupted (Figs. 15–29). Although M 2, M 30 and M-64 had similar configurations of damage, the actual percentages of hair cell destruction and the extent of the basilar membrane involved were more circumscribed (Figs. 16, 27, 31). In M-4 and M 39 damage was often most severe to the first row of outer hair cells in places where the overall destruction was at its greatest from 6.0 mm to 10.0 mm along the basilar membrane. In contrast, the third row of outer hair cells in M 2, M 30, and M-64 was usually the row to have suffered the greatest losses.

In all three groups of monkey inner ears the sensory cells immediately adjacent to regions of damage often appeared abnormal or swollen, even though they had not degenerated. Some were displaced from their normal regular arrangement in even rows. The stereocilia were missing entirely from some outer hair cells and were either distorted or partially

Fig 12 M-4 Longitudinal separation between Hensens cells and Deiters cells (×?00) OHC=outer hair cells HC=Hensen s cells.

Fig 13 M-4 Missing wedges of myelinated radial nerve fibers opposite disrupted organ of Corti (×12)



Fig 14 M-4 Close-up of missing wedge of myelinated radial nerve fibers opposite disrupted organ of Corti (200) NF=missing nerv fibers, OC=missing organ of Corti

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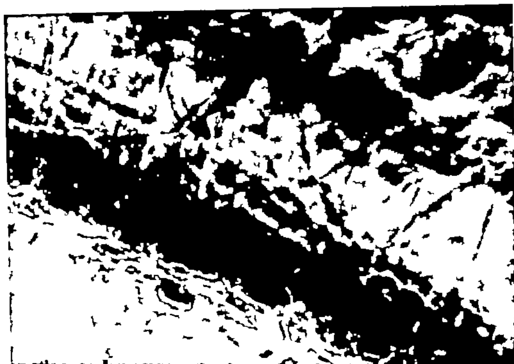


Fig. 17. M-64. Non myelinated radial and spiral tunnel nerve fibers (× 1 000)

Fig. 18. Osmiophilic formations on endolymphatic surface of Reissner's membrane (× 1 000)

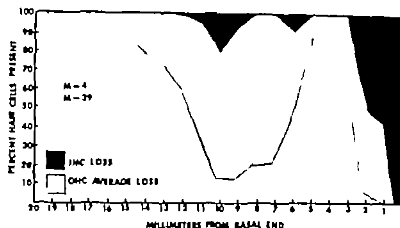


Fig 15 Group III *a* Averaged hair cell los for M-4 and M 39 Outer hair cell los overlaps all inner hair cell loss.

absent on others The finer deails of intracellular changes remain to be determined by electron microscopy

In all the cochleae both radially and spirally running non myelinated nerve fibers (Fig 17) could be observed in the tunnel of Corti Since these seemed to have no regular arrangement it was impossible to judge whether they were depleted in areas of significant outer hair cell loss

Some abnormality was observed in Reissner s membrane in all animals Large rounded osmiophilic cell like clumps of material appeared on the endolymphatic surface of the membranes (Fig 18 A) Dark filaments seemed to protrude from these formations In some areas it was possible to observe the darkly stained clusters of material coming together (Fig 18 B) Other areas disclosed occasional groups of the dark strands or filaments apparently gravitating toward each other (Fig 18 C)

DISCUSSION

The great variability in the sensitivity of the cochlea to acoustic trauma has been noted previously in histological investigations of animal ears (Poche Stockwell & Ades 1969 Stockwell Ades & Engström 1969) Similarly the monkey cochleae showed a wide range in the severity and extent of destruction However certain over all patterns and characteristics of damage emerged

All of the cochleae had some damage in the cecum vestibulare at the beginning of the basilar membrane near the location of the round and oval windows This varied in ex

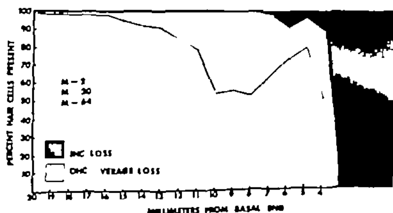


Fig 16 Group III *b* Averaged hair cell los for M 2 M 30 and M-64 Outer hair cell los overl ps all inner hair cell loss

Fig. 19. M-3. Damaged segment of organ of Corti. Note stereocilia of intact inner hair cell (IHC) population. Many missing outer hair cells (OHC) (×400).

Fig. 20. M-3. Near normal segment of organ of Corti adjacent to area shown in Fig. 19 (×400). Level of epi-cal sectioning shows IHC stereocilia only on right side of picture, but all IHC are present.

tent from two to seven millimeters along the *membrane and involved destruction of both* the organ of Corti and the myelinated nerve fibers This held true even for animals with *minimal* degeneration in other areas

In contrast other investigators studying impulse noise have observed no degeneration in this region or degeneration only associated with extensive damage in the more medial regions (Lindquist Neff & Schuknecht 1954 Schuknecht & Tonndorf 1953 Poche Stockwell & Ades 1969 Majeau-Chargois Berlin & Whitehouse 1967 Hamernick Henderson Dosanjh & Sitler 1971) The reason for this difference is obscure but three observations may be relevant (i) The cochlea of man seems to be more susceptible to damage in the base than in more medial areas (Bredberg 1968) Perhaps the monkey shares this characteristic (ii) The peak pressure of this impulse was larger than that reported in *other studies* Under *some circumstances the* area of maximal damage moves basalward with increased intensity of exposure (Stockwell *Ades & Engström 1969) (iii) The* condensation of the impulse was fairly short (60 μsec) For the guinea pig shorter impulses seem to be associated with more damage in the base than longer impulses (Hamernick Henderson Dosanjh & Sitler 1971)

Another common feature was a second region of susceptibility at 8 0 to 10 0 mm along the basilar membrane in the basal turn of the cochlea For two of the animals (M 3 and M 25) this distinction is meaningless since there were no remaining hair cells between the two regions of destruction the first 7 mm of their cochleae were absent In all other animals a small island of less heavily damaged hair cells separated the two regions

Even the minimally involved animals of Group I tended to have sharp peaks of damage in this area In five monkeys (Group III) the damage in this region made a broad notch of destruction This notch was sharply bounded on the basal side by normal organ of Corti On the apical side the change back toward normal was more gradual Lesser *notches of damage in all* animals were always sharply demarcated from normal or near normal organ of Corti (Figs 19 and 20) Abrupt transitions from normal to damaged areas and the sharp localization of such areas have been reported not only for impulse noise (Poche Stockwell & Ades 1969) but also for other types of noise trauma (Stockwell Ades & Engström 1969) The same effect was found in studies of damage due to ototoxic drugs (Stebbins Miller Johnsson & Hawkins 1969) The greater the amount of total hair cell loss the wider the notch of involvement In other words the extent of the damaged area was positively related to the severity of hair cell destruction The sensitivity of the basilar membrane to acoustic trauma at 8 0 mm to 10 0 mm has been pointed out by Schuknecht & Tonndorf (1953) and by Poche Stockwell & Ades (1969) who have studied the effects *of noise on the cochleae of cats and guinea* pigs respectively Bredberg (1968) also noted that this region was subject to degeneration *in the inner ears of humans who had suffered* noise trauma This part of the basilar membrane has been observed to respond maximally to the frequencies between 8 000 Hz and 4 000 Hz. These are the frequencies at which both temporary and permanent shifts in the threshold of hearing are audiometrically recorded when the ear is exposed to intense sound

It would appear that the damage observed in these monkey cochleae was of mechanical origin The shock wave of the impulse initially hit the hook area causing total destruction in this region The main notch of damage at 8 0 mm to 10 0 mm may have coincided with the maximum amplitude of the traveling wave along the cochlear duct with lesser notches distributed in relation to successive peaks of the bulges Békésy (1953) described the vibrations of the cochlea as radial near the base He observed that these changed to longitudinal vibrations at a distance along the basilar membrane determined by the in-

Fig. 21. M-4. Radial gradient of damage. Inner hair cells (IHC) and row 1 outer hair cells (OHC) all present. Row 2 OHC: few missing cells. Row 3 OHC: many missing cells marked by phalangeal scars (arrows). Note stereocilia of IHC and row 1 OHC. P=pillar cells (× 900)

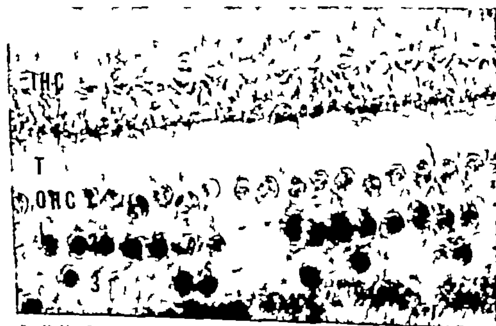


Fig. 22. M-4. Deeper focus of same area as in Fig. 21 showing nuclei of hair cells present. T=tunnel of Corti (× 900)

tensity of the stimulus Such a change of vibratory pattern might increase stress on cochlear structures It might be hypothesized that this transition occurred at 8 0 mm to 10 0 mm from the base in these animals

The longitudinal separation between Hensen s cells and Deiters cells was observed in half the cochleae This split extended over several millimeters in the lower turn basal ward to the 8 0 mm to 10 0 mm section It was more extensive in some monkeys than in others A region of less severely damaged organ of Corti usually paralleled this separation although in some cases the third row of outer hair cells had been torn away together with the Hensen s cells Békésy (1953) first described this phenomenon in studies in which he used intense acoustic stimulation Beagley (1965 *a*) also noted it and suggested it served as a protective mechanism Using electron microscopy he found that the Hensen s cells joined Deiters cells only at the reticular lamina (1965 *b*) Below this junction he observed a canal-like intercellular space Beagley thought the Hensen Deiters separation was due to longitudinal stress Békésy has described the shearing forces of the basilar membrane as more longitudinal in the region of the outer hair cells and more radial nearer the inner hair cells (1951) He observed (1953) that the cochlear vibrations began at the Hensen s cells and passed inward to the outer hair cells Certainly the splitting off of the Hensen s cells from Deiters supporting elements is consistent with the complex patterns of vibrations and stresses that have been reported

After initial loss in the hook area and lower most basal turn the darkly stained myelinated nerve fiber bundles appeared normal with few exceptions This was true even where the organ of Corti was greatly disrupted and in areas where almost all outer hair cells were missing Further absence of nerve fibers was observed in only three monkeys These losses took the shape of narrow wedges with the wider part toward the habenula perforata In two animals (M-4 and M-64) these occurred only where segments of the organ of Corti were completely destroyed However in M-49 two wedge-shaped losses were seen opposite an apparently normal organ of Corti

Inner hair cells seemed to be very resistant to the trauma of impulse noise Poche Stockwell & Ades (1969) also made this observation Inner hair cells were destroyed only in areas where the organ of Corti was totally disrupted In studies of ototoxicity Stebbins Miller Johnsson & Hawkins (1969) found that the relative loss of inner hair cells paralleled and often exceeded the loss of outer hair cells

The reticular lamina also appeared extremely durable It was often intact in areas where all outer hair cells had degenerated The strength of this phalangeal network has been described previously by Stebbins Miller Johnsson & Hawkins (1969) and others The reticular membrane evidently has the capacity to mend itself thus sealing off the endolymph of the scala media from the bodies of the hair cells which are bathed in cortilymph

In this study the radial gradient of involvement of the outer hair cells rows differed from most other reports Poche Stockwell & Ades (1969) observed equal damage to all three rows of outer hair cells in guinea pigs exposed to impulse noise Stockwell Ades & Engström (1969) found that the first row of outer hair cells suffered the greatest destruction in trauma due to intense noise In guinea pigs subject to an intense 500 Hz tone over long periods of time Beagley (1965 *a*) described the damage as decreasing from the first to the third row of outer hair cells In this investigation the third row of outer hair cells was generally the most involved and the first row least (Figs 21 and 22) Bredberg (1968) noted this type of pattern of sensory cell loss in one third of the 41 human cochleae he examined This radial gradient of damage would be consistent with Békésy s observation (1953) that the vibrations of the cochlear structures began with Hensen s cells

The Relationship between Permanent Threshold Shift and the Loss of Hair Cells in Monkeys Exposed to Impulse Noise

by Marilyn Pinheiro, Valdemar Jordan and George A. Luz

INTRODUCTION

Just a few years after psychologists began using conditioned responses to evaluate hearing in animals, the same techniques were employed to study the effects of hazardous noise (Upton 1929, Kemp 1935, Horton 1934). At the same time, new developments in histology (Guild 1921) and electrophysiology (Wever & Bray 1930) allowed scientists several different ways of observing damaged ears. During the last 30 years, there have been many studies relating two of these views, histological and audiometric. Some of the conclusions drawn from similarities in the results of these studies are relevant to the present study of impulse noise damage in rhesus monkeys.

Frequency localization

All investigators found that high frequency tones were detected by basal and low frequency tones by apical cochlear structures. Over a considerable range, a nearly linear spatial distribution on the organ of Corti was found for the logarithmic frequency scale (Schuknecht 1960).

Case Western Reserve University Medical School, Cleveland Ohio 44106

Experimental Psychology Division, US Army Medical Research Laboratory, Fort Knox, Kentucky 40121 USA

In conducting the research described in this manuscript, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

Redundancy

Destruction of hair cells without significant loss of the nerve fiber population and cochlear supporting structures was not always related to a concomitant loss in pure tone hearing sensitivity.

This principle was apparent when Neff (1947) studied the partially sectioned auditory nerve of cats. For example, his Cat 4 showed normal sensitivity for an 8 kHz tone while retaining no more than 20% of the nerve fibers in the region responsible for detection of this signal. Similarly, Elliott (1961), studying mechanically-damaged and noise-damaged cats, found that for the low and middle frequency range, absolute thresholds are normal when only 5 to 10% of the innervation remains, so long as the area of involvement is only a few millimeters long. Elliott also found the same redundancy for pitch discrimination while Elliott & McGee (1965) found it for intensity discrimination. The same principle is reflected in Bredberg's (1968) cross sectional study of hair cell loss in human ears.

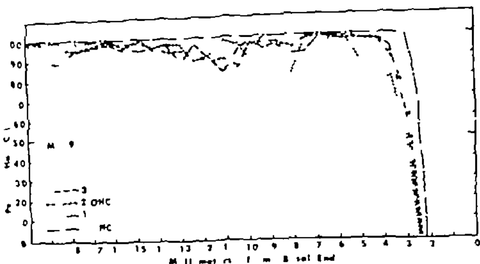
Differences in redundancy as a function of frequency

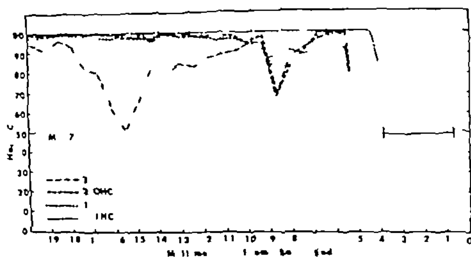
Although this principle cannot be conclusively demonstrated by any one study, it is supported by several. For example, Neff's Cat 8 had a fairly uniform loss of nerve fibers over most of the organ of Corti. Yet it retained normal hearing sensitivity only for 500 Hz and below. The magnitude of hearing loss (in dB) seems to be less after damage to the apical ganglion cells than after damage to the basal ones (as

and proceeded inward to the outer hair cells In this case the outermost third row of sensory cells would receive the greatest vibration and the vibration would diminish as it moved inward toward the modiolus This type of radial gradient of damage in acoustic trauma would also be consistent with the hypothesis that the different rows of hair cells have differential thresholds with the outer most rows having lower thresholds than the inner hair cells (cf Lynn & Sayers 1970)

The origin of the unusual osmiophilic formations on the surface of Reissner s membrane remains obscure The trauma might have caused extrusion of cellular material from the epithelial cells which lined the free endolymphatic surface Possibly these represented a process of phagocytosis in the damaged cochleae

The explanation for the variability in damage to the cochlea by impulse noise or any other type of intense sound exposure is not yet clear However every human and probably every animal especially on the level of the primates differs in many infinitesimal ways from every other One might reasonably speculate that such differences extend to the inner ear Even a minute difference in the alignment of the oval window with the curvature of the lower basal turn of the cochlea would change both the impact of the shock wave of the noise impulse and the distribution of its energy to cochlear structures





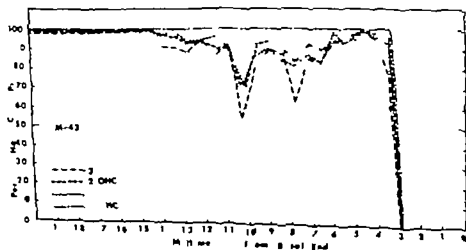


Fig. 23. Hair cell percentage graphs for the three monkeys with the least damage (M-49, M-47 and M-43).

in Elliott 1961) When histological measures were restricted to hair cells rather than gang lion cells the principle was still applicable Thus correlating post mortem hair cell loss with audiometric data of 27 human ears Bredberg (1968) found that up to 40% of the outer hair cells can be lost at 30 mm from the base without a hearing loss exceeding 15 dB at 250 Hz. Yet a 25% loss at 7 mm from the base was related to a hearing impairment of 20–30 dB at 8 kHz

Spread of fields of excitation as a function of intensity

When abrupt transitions between damaged and undamaged elements were achieved by mechanical puncture or ototoxic drugs the slope of the audiogram was shallower than would be expected from a strict frequency localization These shallow audiometric slopes might have reflected the spread in fields of excitation as the intensity of test stimuli was increased (Schuknecht 1960) For lesions in the apical half of the cochlea the ascending audiometric slope was observed to be increasingly steep as the damaged region extended farther basalward Schuknecht found that the relation of the ascending audiometric slopes to extent of damaged area ranged from 0 20 mm/dB in the apex to 0 056 mm/dB in the basal turn of the cochlea Still steeper descending audiometric slopes were recorded by Stebbins Miller Johnsson & Hawkins (1969) for basal lesions in rhesus monkeys

Regions of hypersensitivity

In many audiograms both human and animal a region of depressed hearing sensitivity has been found to be bordered by a region of increased sensitivity at some time after exposure to intense noise Most researchers in psychophysics disregard such negative threshold shifts A decrease in threshold may merely mean the animal has lowered its criterion for a response Without a measure of the animal s criterion such as found in signal detection theory (Green & Swets 1966) there is no way to evaluate a negative threshold shift However the concept of a negative threshold shift is theoretically feasible if auditory neurons are normally masking each other through lateral inhibition (cf Békesy 1967) It follows that the destruction of one set of neurons or hair cells might release a neighboring population from inhibition or masking This theoretical explanation was developed by Carterette (1969) who discussed a number of examples from published studies

The above conclusions are not exhaustive They have been presented to underscore the major features of the present study The last four principles can only degrade the correlation between auditory sensitivity and histological measures In spite of this problem most studies have reported some degree of correlation between histology and behavior This was also true for the present study in which the correlation has been expressed in two ways eta coefficient and visual comparisons

Procedure

Using the place theory of hearing sensitivity thresholds at each frequency tested were related to hair cell percentages at specific distances along the basilar membrane The specific distances representative of the test frequencies were calculated by earlier workers (Békésy & Rosenblith 1951 Schuknecht 1960 and Stebbins Miller Johnsson & Hawkins 1969) These distances along the basilar membrane were related to the test frequencies in the following manner 14 000 Hz at 4 0 mm 10 000 Hz at 6 0 mm 8 000 Hz at 8 0 mm 4 000 Hz at 11 5 mm 2 000 Hz at 15 0 mm and 1 000 Hz at 18 0 mm Since the hair cell percentages represented half millimeter segments each point of comparison actually included 0 25 mm on either side of the reference point

The highest frequency tested in the experimental animals was 14 000 Hz with its place representation at about 4 0 mm along the basilar membrane Since hearing in monkeys

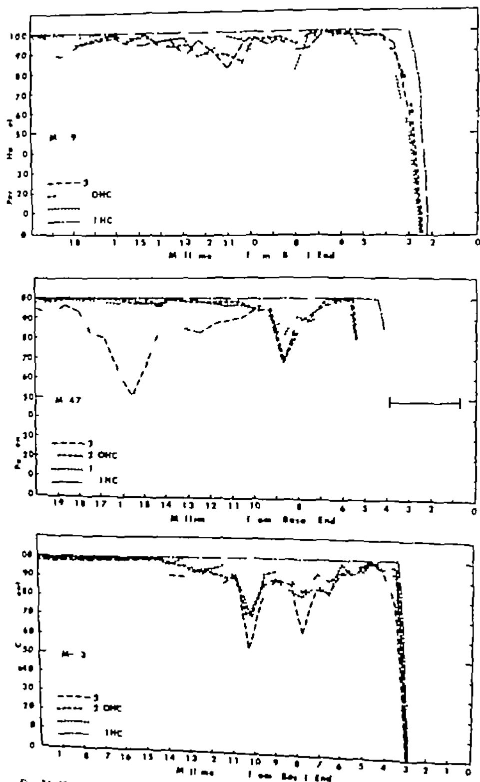


Fig. 21. Hair cell percentage graphs for the three monkeys with the least damage (M-49, M-47 and M-43).

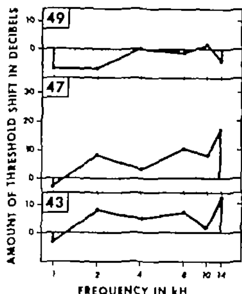


Fig 24 Profiles of hearing loss for the three monkeys *with the least histological damage (M-49 M-47 and M-43)* Negative values indicate an improvement of postexposure threshold over pre-exposure threshold

confined to an area so narrow that it did not affect the audiogram

Monkeys 47 *and* 43 *had both similar hair* cell percentage graphs (Fig 23) and similar threshold shifts (Fig 24) In addition to the *scattered losses* similar to those in M-49 these two monkeys also showed notches in one or more rows of hair cells Presumably these and all other notches of hair cell loss reflected points of maximal stress occurring during im*pulse noise exposure M-47 suffered a notch* of hair cell loss in the third row of outer hair cells at 15 5 mm but this animal had no more hearing loss at the appropriate frequency ? kHz than M-43 The other notches (at 9 mm for M-47 and at 10 5 and 7 5 *mm* for M-43) probably account for the similar threshold

ranges up to 40 000 Hz the complete de*struction of the initial 2 0 mm to 3 0 mm* of the organ of Corti and the accompanying myelinated nerve fibers could not be related to the residual hearing in these animals

Visual comparisons

In the preceding description of the cochlear histopathology the monkeys were divided into three groups according to the variable pat terns of hair cell destruction Each group was related to its respective audiograms

Group I included the three animals (M-43 M-47 and M-49) with the least cochlear dam age *(Fig 23) and the smallest permanent* threshold shifts (Fig 24) M-49 retained nor mal hearing for all test frequencies and per formed even better at 1 and 2 kHz after noise exposure than before Perhaps this improvement reflected a release from inhibition brought about by destruction of the initial 2 5 mm of the organ of Corti Along the rest *of the basilar membrane all inner hair* cells and most outer hair cells were present (Fig 23) The largest outer hair cell loss of about 20% occurred in *the first or innermost row in* the lower basal turn This loss however was

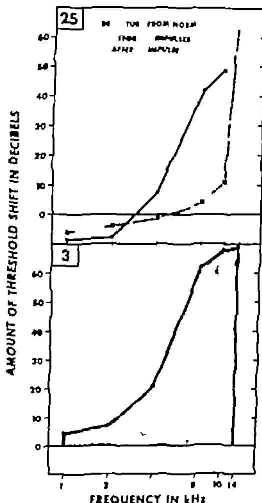


Fig 25 Profiles of hearing loss for two monkeys with damage concentrated in the basal area of the organ of Corti (M 25 and M 3)

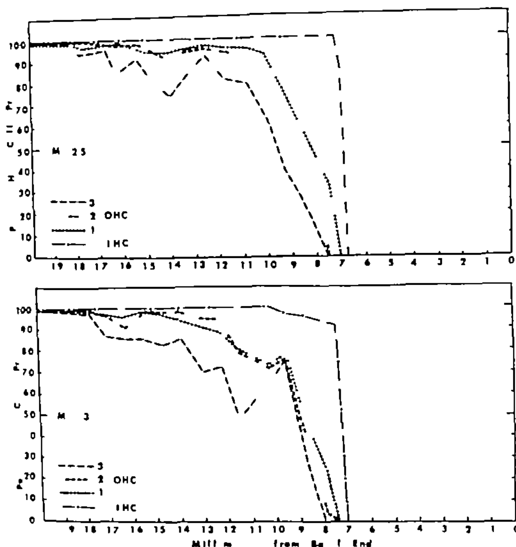


Fig 26 Hair cell percentage graphs from tw monkeys ith damage concentrated in the basal area of the organ of Corti (M 25 and M 3)

hifts at 4 and 8 kHz in these animals The main difference between the two animals hearing was at 10 and 14 kHz where the threshold shift of M-47 was about 5 dB greater than that of M-43 This difference was mirrored by the hair cell percentages M-47 had the larger lesion at the base

Group II included two monkeys whose pre-exposure audiograms were different but whose postexposure threshold shifts were quite similar (Fig. 25) M-3 was one of the nine normal monkeys. The other M 25 was screened out as abnormal because this animal s pre-exposure audiogram showed a 65 dB hearing loss at 12 kHz and no measurable sensitivity at 14 kHz. A comparison of its hearing thresholds with the median threshold values of the group of nine normal monkeys yielded the dotted line in Fig 25 The loss between 10 and 14 kHz was abrupt and reminiscent of that produced by ototoxic drugs (Stebbins Miller Johnsson & Hawkins 1969) Although no past history of ototoxic drug dosage could be established it seemed a likely hypothesis.

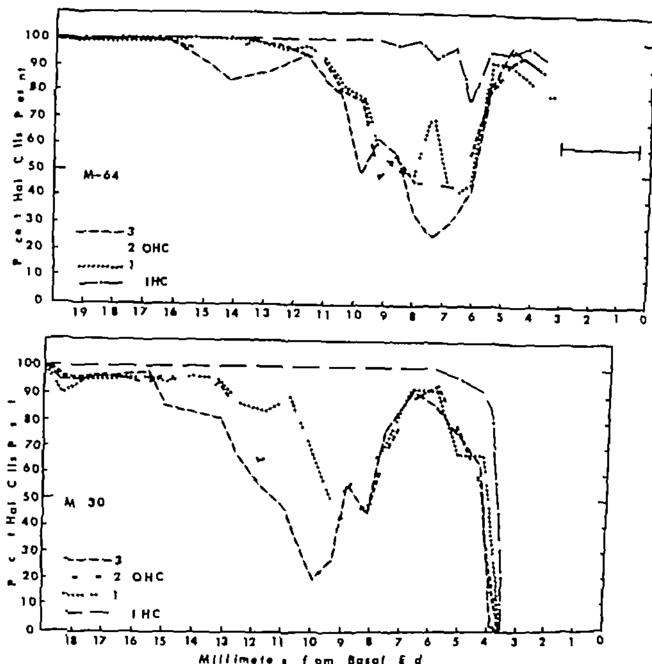


Fig 27 Hair cell percentage graphs for two monkeys with moderate notches in the region of 7 to 11 mm from the base (M-64 and M 30)

(The subject had been inherited from another laboratory.)

One exposure (two impulses) gave M 25 the hearing loss profile drawn in solid line (Fig 25). The slope of this loss profile was about the same as the loss profile for M 3 who received its loss after exposure to 10 impulses. The hair cell percentage graphs were also similar (Fig 26). Each cochlea had a completely denuded area along the first 7 mm from the base. Each had the same gradient of damage (least in the inner hair cells and increasingly more in each successive row of outer hair cells). Both cochlear damage and postexposure hearing loss were somewhat greater in M 3 than in M 25. The 73 dB threshold shift at 14 kHz for M 3 is to be questioned since this animal was undergoing additional loss at this frequency between the 32nd and 64th day after exposure. Hair cells

and nerve fibers might have still been in the process of degeneration (cf Hamernik, Henderson & Sitler 1972)

Of the ten monkeys, these two M 25 and M 3 had results that were most similar to the rhesus monkeys described by Stebbins Miller Johnsson & Hawkins in which ototoxic drugs produced cochleae divided into two regions an apical region with virtually no hair cell loss and a basal region of complete hair cell loss. The difference between results in the two studies was in the size of the area of transition For the ototoxic losses the transition between 95% and 0% hair cells covered 1 to 2 mm. For impulse noise losses in the present study the transition covered about 8 mm Mirroring this difference was a difference in the slopes of the hearing loss profiles for the two groups of monkeys. Conceivably M 25 with its pre and postexposure hearing losses demonstrated both kinds of pathology

Group III included half the monkeys in the study (M 2 M-4 M 30 M 39 and M-64) Each had a major notch of outer hair cell loss falling between 9 and 11 mm from the base (Figs 27 29 and 31) The size of this notch varied For M 30 and M-64 its average depth was 50% (Fig 27) while for M-4 and M-39 its average depth was 85% hair cell loss (Fig 29) It was only this latter group that showed corresponding dips in the post exposure loss profiles (Fig 30)

For the monkeys with the smaller notches of hair cell loss M 30 and M-64 the principles of redundancy with greater redundancy for low frequencies and spread of excitation might have interacted to obscure the relationship between audiometric thresholds and the locus of maximal hair cell loss Thus both monkeys showed increasing loss as a function of frequency but neither showed an audiometric dip (Fig 28) M-64 with a notch of hair cell loss centered about 3 mm closer to the base than M 30's, had less threshold shift at 1 and 2 kHz and a greater shift at 14 kHz than M 30

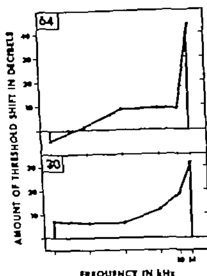


Fig 28 Profiles of hearing loss for two monkeys with moderate notches in the region of 7 to 11 mm of the base (M-64 and M-30)

For the two animals with the deepest notches of hair cell loss the width of the notch seemed to affect the profile of loss (Fig 30) For M-4 with a notch of hair cell loss that was narrow and centered at 9 mm, hearing loss was maximal (34 dB) at 8 kHz with much less hearing loss at adjacent frequencies (4 and 14 kHz) In contrast, M 39 had a greater hearing loss (47 dB) spread over two octaves (4 and 8 kHz) M-4 had a large notch of missing inner hair cells which might have been related to the large postexposure hypersensitivity developed in this animal (cf theoretical formulation of Lynn & Sayers 1970) At 64 days after exposure hearing sensitivity thresholds were improved by 10 dB at 1 kHz and 12 dB at 2 kHz.

The loss profile for the fifth animal, M 2, represented the transition between the less severe profiles of M 30 and M-64 and the "dip profiles of M-4 and M 39 Like M 30 and M-64 the hearing loss was greatest at the high frequencies of 10 and 14 kHz, but also included 4 and 8 kHz (Fig. 31) Unfortunately a significant area of the outer hair cells was inadvertently destroyed in the surgical preparation of the cochlea of this animal However hair cell counts were interpreted as indicating that this area had outer hair cell

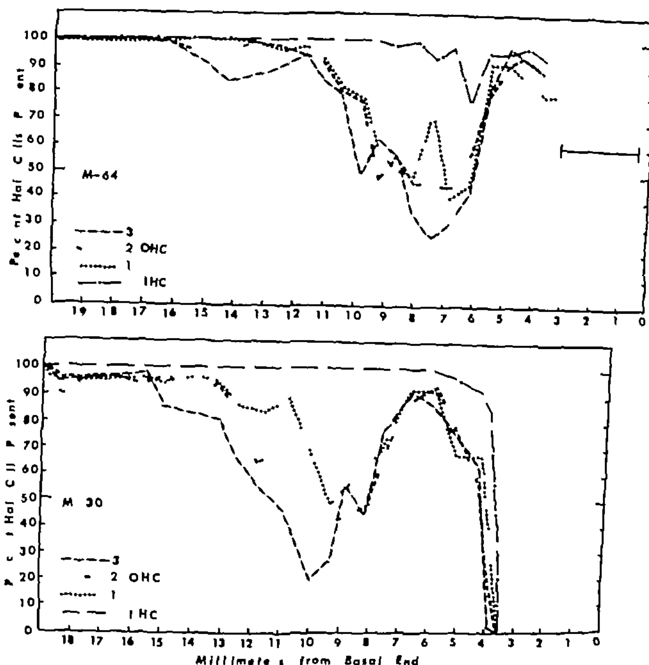


Fig 27 Hair cell percentage graph for two monkey with moderate notches in the region of 7 to 11 mm from the base (M-64 and M 30)

(The subject had been inherited from another laboratory)

One exposure (two impulses) gave M 25 the hearing loss profile drawn in solid line (Fig 25) The slope of this loss profile was about the same as the loss profile for M 3 who received its loss after exposure to 10 im pulses The hair cell percentage graphs were also similar (Fig 26) Each cochlea had a completely denuded area along the first 7 mm from the base Each had the same gradient of damage (least in the inner hair cells and increasingly more in each successive row of outer hair cells) Both cochlear damage and postexposure hearing loss were somewhat greater in M 3 than in M 25 The 73 dB threshold shift at 14 kHz for M 3 is to be questioned since this animal was undergoing additional loss at this frequency between the 32nd and 64th day after exposure. Hair cells

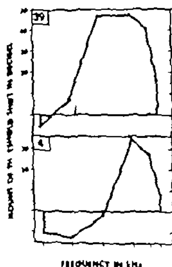


Fig 30 Profiles of hearing loss for two monkeys with larger notches in the region of 7.5 - 11 mm of the base (M 4 and M 39)

been used over the range of 4 to 10 kHz some of the other notches of hair cell loss might have been mirrored in the profile On the other hand the redundancy spread of excitation and release from inhibition mentioned in the Introduction might still have masked the notches of hair cell loss even in a finer-grained audiogram Using pure tones separated by only 0.5 octave behavioral audiograms do not reflect narrow wedges of hair cell loss in the chinchilla (Eldredge 1972)

Admittedly it was difficult to predict the state of an individual animal's hair cells by studying his pure tone audiogram Hearing losses seemed to be a function of both the percentage and the extent of the hair cell loss along the basilar membrane However when data were pooled from all animals there was

Fig 31 Hair cell percentage graph and profile of hearing los for M 2. This subject's audiogram represents a transition between those of M 30 M-64 and those of M-4 M-39

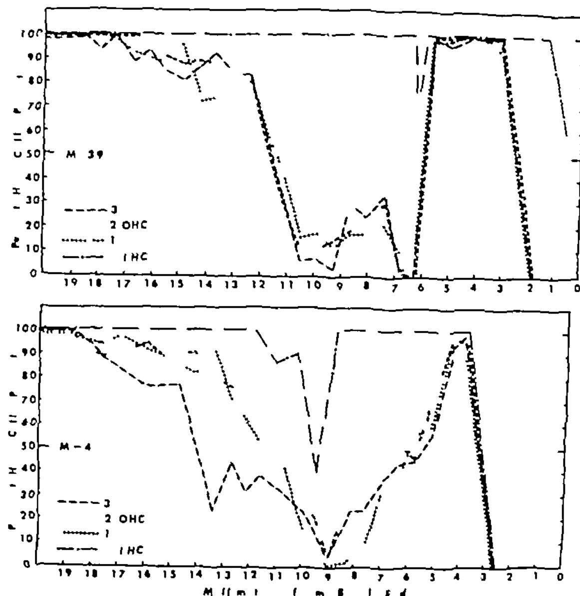


Fig. 39. Hair cell percentage graphs for two monkeys with large 4 kHz notches in the region of 7 to 11 mm of the base (M-4 and M-39).

degeneration. This was deduced from the observation that more outer hair cells were present at the basal edge of the artifact than at the apical edge. Inner hair cells and myelinated nerve fibers were present in the artifact region, so that the organ of Corti was not entirely destroyed by acoustic trauma. The 18 dB SPL hearing threshold at 4 kHz probably corresponded to the average 20% outer hair cell loss between 11.0 mm and 13.5 mm.

Statistical comparison

The particular noise impulses used appeared to damage the monkey cochleae in two areas: (1) at the base of the cochlea and (2) somewhere between 7 and 11 mm from the base. In severely damaged monkeys (M-25 and M-3) the basal lesion was expanded into the second region. For these monkeys, the graphs of the hair cell percentages were easily matched to the shape of the loss profiles. However, in monkeys who suffered varying amounts of hair cell loss in both regions, there was often a mismatch between the shapes of the hair cell graphs and the profiles. For instance, a small hair cell loss (50%) at 7 to 11 mm could not be matched to a dip in the hearing loss profiles. If more pure tones had

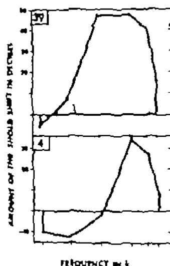


Fig. 30. Profiles of hearing loss for two monkeys with largest notches in the region of 7.1–11 mm of the base (M-4 and M-39).

been used over the range of 4 to 10 kHz, some of the other notches of hair cell loss might have been mirrored in the profile On the other hand the redundancy spread of excitation and release from inhibition mentioned in the introduction might still have masked the notches of hair cell loss even in a finer-grained audiogram Using pure tones separated by only 0.5 octave behavioral audiograms do not reflect narrow wedges of hair cell loss in the chinchilla (Eldredge 1977)

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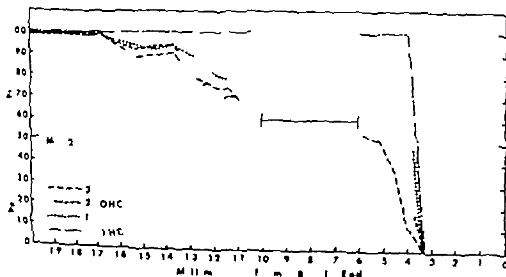


Fig. 31. Hair cell percentage graph and profile of hearing loss for M-2. This subject's audiogram represents a transition between those of M-30, M-64 and those of M-4, M-39.

a statistically significant relationship between hearing level and hair cell loss The eta coef ficient (Downie & Heath 1965) was computed for the averaged outer hair cell percentages (at the places on the basilar membrane thought to be representative for each frequency) and the hearing thresholds at each frequency The resulting correlation ratio was 0 85 The F value was significant beyond the 0 01 level of probability Therefore the percentage of outer hair cells present was significantly related to the hearing threshold seen at 64 days after noise exposure The value of this correlation coefficient is nearly equal to that reported by Miller Watson & Covell (1963) (r=0 83) for the cat

General Summary

Eleven rhesus monkey surgically deafened in the right ear were tested in a shuttlebox for pure tone sensitivity at 1 2 4 8 10 and 14 kHz The behavioral technique, avoidance conditioning was under the control of a human observer who used a descending method of limits to determine threshold Using these methods nine of the 11 appeared to have normal audiograms the tenth had a high frequency loss of unknown origin The eleventh did not learn the avoidance task and was withdrawn from the experiment

Following this initial audiometric testing, all 10 monkeys were exposed to two impulses of 168 dB peak SPL and tested for temporary threshold shift (TTS) In addition the nine normal monkeys were exposed to 12 min of recorded tank noise a second and a third "2-impulse exposure and a 10-impulse exposure (in that order) Two animals received a final 20-impulse exposure TTS was evaluated after each exposure and time was allowed for recovery between exposures

For the tank noise monkeys showed a greater TTS than a group of new recruits exposed to the same noise After tank noise TTS recovered as a linear function of the logarithm of recovery time but after impulse noise recovery was much more variable. In some cases more threshold shift was seen at an hour after exposure than at 30 min after exposure

The dynamics of the ears seemed to change during the course of repeated exposures. For example seven of the nine monkeys showed less TTS at 5 min after the second than at the same time after the first exposure to tank noise The correlation between TTS_5 for these two exposures was −0 74 For impulses eight of nine monkeys showed less absolute shift at 1 kHz after the third 2-impulse exposure than after the first However six of the nine animals showed more absolute shift at 8 and 14 kHz after the third 2-impulse exposure At the end of all exposures eight of the original 10 showed increased sensitivity at 1 kHz.

Following the final impulse exposure recovery of threshold was studied for 64 days. Although median shift was greatest at 8 or 10 kHz during the first eight days it was greatest at 14 kHz at the end of 64 days. Only two monkeys suffered a maximum dip in their audiogram at 4 or 8 kHz. Correlations made between the amount of permanent threshold shift (PTS) seen at 64 days and the TTS seen after the first 2-impulse exposure were close to zero

The second laboratory perfused and dissected the cochleae and made them into surface preparations Sections were studied under the phase contrast microscope and hair cell counts were made without knowledge of the behavioral audiograms Two areas of damage were noted, one in the cecum vestibulare at the beginning of the basilar membrane and the other at 8–10 mm from the base. For the latter transitions from normal to damaged hair cells were more abrupt on the basal than on the apical side. Damage tended to be greatest in the third row of outer hair cells and least in the inner hair cells. When the organ of Corti remained partially intact the inner hair cells usually appeared to be normal The reticular lamina was extremely durable In half of the cochleae a longitudinal separation between Hensen s cells and Deiters cells was observed Darkly stained myelinated nerve fibers were missing in the hook area and lowermost turn of all ears When seg-

ments of the organ of Corti were destroyed narrow wedges of myelinated nerve fibers were also missing However in one ear two wedge-shaped losses were seen opposite an apparently normal organ of Corti

Based on the calculations of earlier workers sensitivity thresholds at each frequency tested were related to hair cell percentages at specific distances along the basilar membrane The correlation between the averaged outer hair cell loss of the 0 5 mm segments and threshold was 0 85 When notches occurred at 8–10 mm of the base a hearing loss of greater than 15 dB at 2 4 or 8 kHz was found only when damage to one of the rows of outer hair cells exceeded 80% in at least one 0.5 mm segment

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SUPPLEMENT 313

Postnatal Development of the Lateral Vestibular Nucleus (Deiters' Nucleus) of the Rat

A light and electron microscopic study

BY

EERO KARHUNEN

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ACTA OTO LARYNGOLOGICA

SUPPLEMENT 313

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From the Department of Anatomy
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HELSINKI 1973

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SUPPLEMENT 515

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University of Helsinki, Finland

HELSINKI 1975

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INTRODUCTION

The lateral vestibular nucleus is an important vestibular relay station. It is the sole origin of the massive vestibular pathway to the various levels of the spinal cord. It contributes strategically to the control of muscular coordination and maintenance of equilibrium. Recent fine structural studies have essentially increased our knowledge concerning its structure, but only two investigations have been reported on the pre- and postnatal development of this nucleus. It has been shown in the chick that the cells of this part of the vestibular nuclear complex are derived from the medial part of the matrix of the basal lamina, while the cells of the other vestibular nuclei originate from the dorsal part of the alar lamina (Vraa-Jensen, 1956). Only one investigation (Hauglie-Hanssen, 1968) deals with the structure of the nucleus in the newborn. Using various modifications of the Golgi method this paper showed that the cyto- and fibroarchitectures of the lateral vestibular nucleus in newborn kittens, rats and mice are quite similar to the corresponding adult structures. However, the postnatal ultrastructural development of the nucleus has not been studied systematically age group by age group. It seems reasonable to assume that a thorough understanding of the fine structure of the neurons and the distribution of nerve endings, as well as the formation of synapses at various stages of development would provide a means of better understanding the physiological differences at different developmental stages. A basis would thus be created for neurophysiological studies on the development of the vestibular function.

The postnatal growth and development of mammalian nerve cells in general is not completely understood. The same is true for the development and formation of synapses in the central nervous system, where the available data is meagre. It therefore also seemed to be of great general interest to elucidate the morphological events in the lateral vestibular nucleus from birth to adult age, paying attention in particular to the postnatal development of the nerve cells, structure of the neuropil, synaptic connections, glial cells, and their relations to neurons.

INTRODUCTION

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Abbreviations used in figures

AH	axon hillock
As	astrocyte
Ax	axon
CAx	central axon
Cy	cytoplasm
Den	dendrite
Dgc	dark glial cell
GN	giant neuron
Go	Golgi apparatus
IS	initial segment of axon
LaAT	large axon terminal
Lgc	light glial cell
MN	medium-sized neuron
Ngc	new glial cell
Nu	nucleus
Ol	oligodendrocyte
RER	rough endoplasmic reticulum
SlAT	slender axon terminal
SmAT	small axon terminal

In the last century Deiters described a group of large nerve cells in the brain stem of man and certain other mammals. The same cellular group has been described later by numerous investigators under the name of Deiters' nucleus or nucleus vestibularis lateralis (the lateral vestibular nucleus) of Deiters. Other names used in the literature are grosszelliger Vestibularkern and noyau à grandes cellules de l'acoustique. Both the terminology employed by the earlier authors and their descriptions of the vestibular nuclei contain discrepancies and cause confusion. While in 1887 von Monakow defined as the nucleus of Deiters that part of the vestibular nuclear complex in which the giant nerve cells undergo chromatolysis following lesions at the rostral level of the spinal cord, a definition according to which this nucleus comprises extensive parts of the entire vestibular nuclear complex was adopted by many other anatomists (e.g. Lewy 1910; Fuse 1912; Winkler, 1913–14; Winkler & Potter 1914; Meessen & Olszewski, 1949). The term was used in the restricted sense by Sabin (1897), Ramón y Cajal (1896, 1909), and Ariëns Kappers et al. (1936). This is also in agreement with the modern definition (Brodal & Pompeiano, 1957).

According to Brodal & Pompeiano (1957) in the young cat the lateral vestibular nucleus of Deiters includes that part of the vestibular nuclear complex which is characterized by the presence of giant cells of Deiters. These giant cells are usually multipolar and show considerable variations in size and shape. They are more numerous and somewhat larger in the dorsocaudal than in the rostroventral part of the nucleus. The lateral vestibular nucleus also contains smaller cells of various sizes. There are both medium-sized, frequently oval or spindle-shaped cells and small round or oval cells. These types are more numerous in the rostral part of the nucleus. At the lateral border of the nucleus there is a small group of medium-sized cells, labelled l. Just as previously Ramón y Cajal (1909) and Fuse (1912), Brodal & Pompeiano suggested that the interstitial nucleus of the vestibular nerve of Cajal (noyau interstitiel du nerf vestibulaire) can be an aberrant part of Deiters' nucleus. The cells in this site are chiefly elongated and medium-sized, but giant cells of the type found in the lateral vestibular nucleus also occur. In addition to the above-mentioned criteria, Brodal & Pompeiano proposed certain landmarks by which the lateral vestibular nucleus can be distinguished from other parts of the vestibular nuclear complex and the neighbouring areas of the brain stem. Furthermore, they pointed out that of the whole vestibular complex, this nucleus appears in many respects to be the part most clearly characterized as a separate unit. Besides having a specific cytoarchitecture it appears to differ from the other classical vestibular nuclei

Abbreviations used in figures

AH	axon hillock
As	astrocyte
Ax	axon
CAx	central axon
Cy	cytoplasm
Den	dendrite
Dgc	dark glial cell
GN	giant neuron
Go	Golgi apparatus
IS	initial segment of axon
LaAT	large axon terminal
Lgc	light glial cell
MN	medium-sized neuron
Ngc	new glial cell
Nu	nucleus
Ol	oligodendrocyte
RER	rough endoplasmic reticulum
SlAT	slender axon terminal
SmAT	small axon terminal

I thei exhausti e investigations of the lateral vestibular nucleus Mugnaini et al. (1967 b) used both light microscopy of semithin sections stained with toluidine blue and electron microscopy f the ultrastructure in both normal dult cats and after damage to the primary estibula fibres (Mugnaini et 1 1967 a) and the cerebello-estibula fibres (Mugnaini & W lberg, 1967) The estibular nuclei in the rat were systematically investigated for the first time by Sotelo & Palay (1968) who described the lateral estibular nucleus f the adult rat mainly on the fine structural level but also on the basis of light microscopy of semithin toluidine blue sections using the neurofibrillary methods of both Golgi-Rio Hortega and Cajal. In a second study by the same authors (1970) the synaptic structure f the lateral vestibular nucleus f the dult rat was described in great deta l and the findings were compared with the result previously reported in the cat (Mugnaini et al., 1967 b) Significant d fferences were observed between these two animal species with regard to the synaptic organization of corresponding nuclei A third study by Sotelo & Palay (1971) dealt with the altered axons and axon terminals normally occurring in the lateral est bul nucleus.

with regard to embryological derivation (Aras Jensen 1956). It also stands out as a particular entity more clearly than the remaining nuclei with regard to afferent and efferent fibre connections. Functionally too, the lateral nucleus is a relatively independent part of the vestibular nuclear complex. It receives important afferent fibres from the vestibular apparatus, the cerebellum and the spinal cord. The course and central termination of the primary vestibular fibres were described by some early anatomists (Koelliker 1891, Held 1892, Ramón y Cajal 1909, Leidler 1914) and later by Lorente de Nó (1933) and Walberg et al. (1958). More recently Stein & Carpenter (1967), Mugnaini et al. (1967 a) and Gacek (1969) have supplied significant detailed information on the origin, course and termination of the primary vestibular fibres. Although it had long been known that the cerebellar cortex and nuclei send afferent fibres to the vestibular nuclei (e.g. Allen 1924, Hohman 1929, Rasmussen 1933, Dow 1936, 1938, Jansen & Brodal 1940, Jansen & Jansen 1955, Thomas et al. 1956) Walberg & Jansen (1961), Walberg et al. (1962) and Mugnaini & Walberg (1967) gave a minute description of the cerebellovestibular fibres and showed that the lateral vestibular nucleus is the main terminal area of these fibre connections. The third well known afferent fibre connection to the lateral vestibular nucleus consists of the spinovestibular fibres mainly originating from the lumbar cord. It was first described by Thiele & Horsley (1901), later by Hashimoto (1928) and Johnson (1954) and in greater detail by Pompeiano & Brodal (1957).

The lateral vestibular nucleus sends efferent fibres to the vestibular apparatus, to various levels of the spinal cord and to the oculomotor nuclear complex, possibly by passage to the cortical vestibular centres. The lateral vestibular nucleus is the only one of the four classical vestibular nuclei which probably sends efferent fibres within the vestibular nerve to the vestibular neuroepithelium of the labyrinth (Gacek, 1965). On the basis of earlier studies by Rasmussen (1946, 1953) and Wersäll et al. (1951) this efferent fibre system was described by Petroff (1955) and in more detail by Rasmussen & Gacek (1958) and Gacek (1965). Supplementary investigations were published by Dohlman et al. (1958), Carpenter et al. (1959), Rossi & Cortesina (1962), Hilding & Wersäll (1962) and Iurato et al. (1971). The main efferent pathway of the lateral vestibular nucleus is the vestibulospinal tract derived exclusively from this nucleus and extending to the lumbar cord. This efferent fibre connection has been known for a long time (Monakow 1885, Lewandowsky 1904, van Gehuchten, 1904). Later it has been studied by numerous authors (e.g. Foerster & Gagel 1932, Buchanan 1937, Cooper & Sherrington, 1940). More recently Pompeiano & Brodal (1957) and Nyberg-Hansen & Mascitti (1964) have described the origin, course and termination of the vestibulospinal tract in greater detail. The third efferent pathway of the lateral vestibular nucleus, i.e. the fibres to the higher levels of the brain, has been described by Muskens (1915–14), Buchanan (1937), Szentágothai (1950, 1964) and recently in detail by Gacek (1971). The ascending tract of Deiters to the oculomotor nuclei has been thoroughly investigated but knowledge of the other termination areas is fragmentary. The remaining afferent and efferent fibre connections of the lateral vestibular nucleus of Deiters have scarcely been described. The intrinsic fibre connections within the entire vestibular nuclear complex are still obscure.

Although the fibre connections of the vestibular nuclei have been extensively studied in recent years, only a few reports deal with their fine morphological structure

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microscope to check the position of the lateral vestibula nucleus. This area was further trimmed, and when the nucleus was found, serial sections 1 µ in thickness were made in all three directions (transverse, sagittal and frontal) for light microscopy and thin adjacent sections for electron microscopy were cut on an LKB or Reichert ultrotome with glass knife. Afterstaining was performed on grids with lead citrate (Reynolds, 1963), uranyl acetate (Watson, 1958) or both. The specimens were examined and photographed with an AEI EM 801 or Philips EM 300 electron microscope.

Light micrographs magnified 400 × were chiefly used in this study In addition, light micrographs f lower magnification (120 × and 250 ×) were used. In order to btain better view of the various levels of direction of the nucleus, the micrographs were taped together to montages. Glial cells per unit f surface area were counted on these montages.

Neurons and glial cells were measured on electron micrographs magnified about 8 000 and 20 000 × (negative 4 000 and 10 000) which were taped together to montages. Each montage mostly showed the soma of one neuron and the immediately surrounding tissue In the various age groups about 10 each of giant, medium-sized and small neurons and glial cells f arious types were measured. The results given express the ariation in maximum and minimum diameter of the cell body and nucleus in 10 cells of each type, without processes. In all cells measured, the transverse section was made through the nucleolar plane.

The presynaptic axon terminals of the neurons f various sizes were classified by size and shape including their functional zones, as suggested by Sotelo & Palay (1970), and the terms axon terminal and synapse are used in accordance with the definition given by Peters & Palay (1966) The number f various axon terminals per neuron was calculated for the different categories f neurons in the same material as the neurons and nuclei were measured. The results express the variation in number of various presynaptic terminals per cross-section f cell. Furthermore the number of synapsing axon terminals per length unit of perikaryal or dendritic surface area was calculated in the same material.

MATERIAL AND METHODS

A total of 274 Sprague-Dawley albino rats of both sexes were used in this investigation. The age distribution was as follows: 8 newborn, 6 four-day-old, 7 seven-day-old, 8 ten-day-old, 5 twenty-day-old, 6 thirty-day-old and 231 adult rats. Of the adult rats 54 were used in the electron microscopic studies. The remainder were used in various light microscopic investigations, serving as a thorough introduction into the structure of the entire vestibular nuclear complex. The newborn rats, though a few hours old, were always fixed on the day they were born. Animals over three months old were considered adult.

All rats were perfused under ether anaesthesia via the left ventricle of the heart. Simultaneously the two jugular veins were opened and the abdominal aorta was closed by forceps to make perfusion fixation more effective. The perfusion fixation procedure was the same as has previously been described in detail by Reichardt (1969). The fixation fluid consisted of 3.5 per cent formaldehyde pro analysi grade (E. Merck AG, Darmstadt) buffered with 0.075 M phosphate to pH 7.4. The perfusion time was 15 minutes.

The brain stem with the cerebellum was dissected out in one block and then immediately placed under the stereomicroscope. The cerebellum was removed by dissection of the cerebellar peduncles with scissors as proximally as possible in order to avoid damage to the vestibular nuclei. The various parts of the fourth ventricle of the brain with their anatomical details were identified on inspection of the dorsal aspect of the preparation (Wünscher et al. 1965). The brain stem was transversely cut with a razor blade at the level of the aqueduct of Sylvius. The genu and fibres of the facial nerve could then be identified because the plane of dissection ran through the caudal part of the superior vestibular nucleus and the rostroventral part of the lateral vestibular nucleus. A couple of slices of the vestibular nuclear region about 1 mm thick were cut with the razor blade transversely in the caudal direction and freed from tissues not belonging to the vestibular nuclei and their immediate surroundings. These specimens, which consisted of the lateral vestibular nucleus and immediately adjacent tissues, were immersed overnight in the above-mentioned fixative. The surrounding tissues served as landmarks for the identification of the various parts of the lateral vestibular nucleus.

The tissue pieces were then washed for two hours in several changes of ice-cold 0.075 M phosphate buffered to pH 7.4 and refixed for two hours in 2 per cent OsO. Dehydration was carried out in a graded ethanol series, after which the specimens were embedded in Epon (Luft 1961) or in Epon Araldite ([illegible]). Sections 1 μ thick were stained with toluidine blue and examined under the light

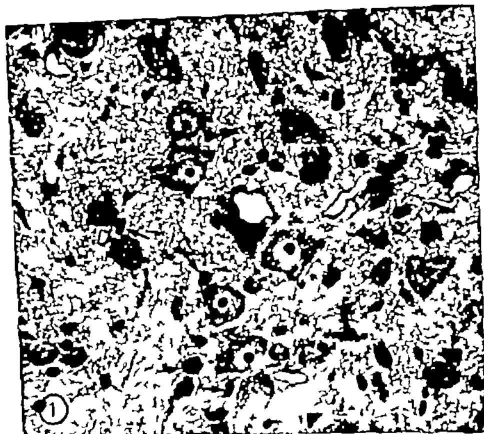


Fig. 1. — Light microscopic view of the dorsocaudal part of the lateral vestibular nucleus of newborn rat. Giant neurons in groups predominate. Note the satellite position of light glial cells, marked by big arrows, and the position and grouping tendency of dark glial cells, marked by small arrows. Toluidine blue stained Epon-Araldite section. ×400

Such communications could be seen in a number of 7—8 per cross-section of medium-sized cell. Nuclear indentations were common in neurons of all sizes.

The Nissl substance was coarse, scattered and randomly arranged. It was usually dispersed all over the cytoplasm, although in some cells the largest and heaviest stained clumps were peripherally located. This applied to neurons of all sizes, but in particular to the giant ones, which contained Nissl substance in considerably greater amounts than the medium-sized and small neurons. It should be emphasized that the location of the Nissl substance peripherally in the cytoplasm seemed to be due to chance. The cytoplasm of the giant neurons, in particular, invariably contained light vacuoles around the nucleus, varying in shape.

The giant cells did not vary very much in shape. They were usually either spheroid or polygonal, but also multipolar forms occurred. The large nucleus was often peripherally situated. The cytoplasm of the giant neurons was extensive, but that of the medium-sized and small neurons was generally scanty. In the medium-sized neurons sometimes widening to a perikaryon containing an abundance of cell organelles.

RESULTS

Newborn rats

GENERAL FEATURES

Neurons of various sizes were evenly distributed throughout the lateral vestibular nucleus, though giant cells predominated in its dorsocaudal part (Fig. 1) The neurons mainly occurred in groups of 2–5 The neuropil was wide pale and homogeneous in appearance Glial cells were present in slightly lesser number than neurons. The glial cells could be divided into two distinct types. There was a smaller variety "dark glial cells" with nuclei heavily staining with toluidine blue Often occurring in groups of 3–5 they were uniformly distributed over the neuropil. This type which predominated, was seldom encountered close to neurons "Light glial cells" on the other hand were often found in the immediate vicinity of neurons. These cells had larger and lightly staining nuclei. Besides glial cells, nerve fibres of various sizes and small capillaries were distinguished with the light microscope in the weakly staining neuropil.

Ultrastructurally unmyelinated nerve fibres, often identified as axons, coursed in various directions. The majority of these nerve fibres were thin and disposed in bundles of various sizes. The thinnest fibres had a diameter of 0 1–0 4 µ Considerably thicker nerve fibres were also relatively numerous. The thickest measured 1 0–1.5 µ in diameter These were still more often identified as axons. They also differed from the thinner nerve fibres by frequently establishing synapses with one another and also with the dendrites in contact with them. The small nerve fibres seemed to be the site of synapses considerably less often. Glial cells with a scanty cytoplasm and clumsy extensive processes surrounded the main bulk of neurons.

NEURONS

Their nuclei were large, occupying over half of the surface area even in giant neurons, and spherical or elongated in shape Because of the considerably heavier peripheral staining of the nucleoplasm the boundary to the cytoplasm was occasionally indistinct, though mostly readily distinguished. At the centre of the nucleus a large well defined nucleolus was clearly seen against the pale background.

The chromatin was in general uniformly distributed throughout the nucleoplasm In the medium-sized and small neurons the two layers of the nuclear membranes were often more widely separated than usual and formed perinuclear cisterns, frequently communicating with the tubules of the rough endoplasmic reticulum.

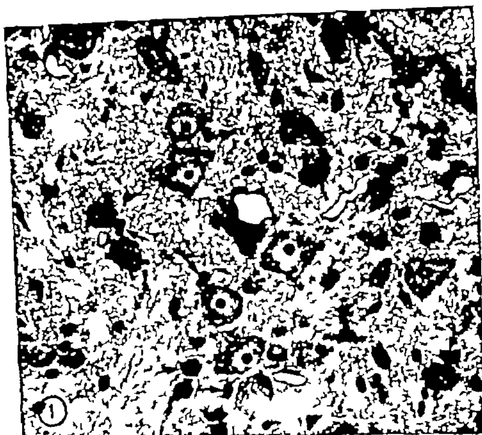


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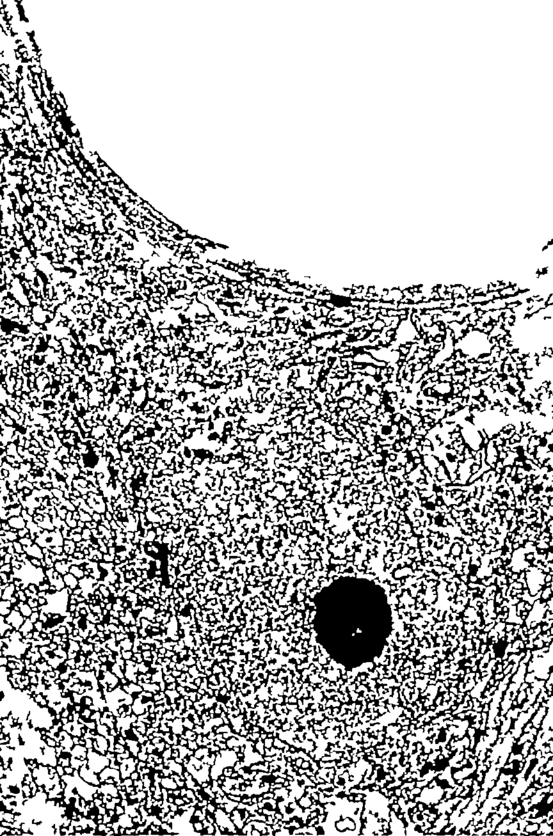
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The giant cells varied in diameter from 20—30 μ their nuclear diameter from 15—20 μ The corresponding variations in the small neurons were from 5—15 μ and from 5—10 μ Cells measuring from 10—20 μ in longitudinal and transverse sections, with nuclei varying from 10—15 μ in diameter were considered medium sized

Cytoplasmic organelles such as the rough endoplasmic reticulum were sparse and scattered throughout the cytoplasm in the small and medium-sized neurons in the giant cells they were relatively abundant In all neurons the tubules were thick, short and often displayed swellings. In general they were disposed randomly and not in anything like parallel array The ribosomes were numerous and mostly arranged in rosettes. Their distribution in the cytoplasm was relatively uniform, although they occurred in greater number in close vicinity to the endoplasmic reticulum. Large clusters, obviously consisting of individual ribosomes, were occasionally seen in the cytoplasm of all neurons. There were numerous well developed Golgi complexes with flat or bulging cisterns in the giant and medium sized cells (Fig 2) The relatively few mitochondria were large, varying in length from 0.2—2.5 μ The few neurofilaments seemed to be located at random among other organelles, most frequently at the base of dendrites. In cross-sections of the giant and medium-sized neurons the neurofilaments sometimes seemed to run roughly parallel with one another in bundles, occasionally containing even a great number of filaments. Microtubules were infrequent, although a relatively constant finding in the peripheral cytoplasm of the larger neurons. In this age group subsurface cisterns were seen only occasionally in the giant cells. By contrast the thorns characteristic of the giant and medium sized cells of Deiters were fairly numerous They were small spines exclusively containing ribosomes scattered over the cytoplasm and never disposed in clusters. The thorns were frequently covered by axon terminals of various sizes, which synapsed on them Stacks of cisterns of endoplasmic reticulum were also observed in the cytoplasm of the medium sized neurons (Fig 5)

SYNAPSES

Axo-somatic synapses

The cytomembranes of both the giant and medium-sized neurons were almost completely covered by nerve endings of various sizes. Nerve fibres by passage dendrites and perikarya or processes of glial cells and sometimes capillaries were in immediate contact with the neuronal cytomembranes. Both large and small axon terminals were seen in great number but no clearly slender terminals. Small nerve endings predominated on the neurons of all sizes It was noteworthy however that although axon terminals of various sizes occurred in a number of 30—50 per giant cell profile only a small proportion of them synapsed on the neuron. The number of terminals

Fig — Electron microscopic general view of medium-sized neuron in Deiters nucleus of a newborn rat Figs 1 and 2 represent semithin and ultrathin section respectively adjacent to each other The neuron shown in this electron micrograph is marked MN in Fig 1 Only two axon terminals (thick arrows) synapse on the cell body of this neuron Note the well developed Golgi apparatus with flat cisterns × 8000.

Table I. *Formation of axo-somatic synapses in the lateral vestibular nucleus of the rat.* Abbreviations: LaAT large axon terminals. SlAT slender axon terminals. SmAT small axon terminals

Type of neurons	Giant neurons		Medium-sized neurons		Small neurons	
Age in day	Total number of synapsing axon terminals per neuron profile (mean value)	Different types of axon terminals	Total number of synapsing axon terminals per neuron profile (mean value)	Different types of axon terminals	Total number of synapsing axon terminals per neuron profile (mean value)	Different types of axon terminals
Newborn	4–7 (5)	LaAT 3–6 SlAT – SmAT 1–2	2–4 (3)	LaAT 2–3 SlAT – SmAT 0–2	0–1 (<1)	LaAT – SlAT – SmAT 0–1
4 day	10–25 (15)	LaAT 3–6 SlAT – SmAT 7–18	5–12 (8)	LaAT 2–4 SlAT – SmAT 3–9	0–5 (2)	LaAT – SlAT – SmAT 0–5
7 days	21–30 (23)	LaAT 3–5 SlAT 1–3 SmAT 14–22	10–16 (13)	LaAT 2–5 SlAT 0–2 SmAT 7–12	0–3 (2)	LaAT – SlAT – SmAT 0–3
10 day	21–34 (27)	LaAT 4–6 SlAT 2–3 SmAT 13–21	14–21 (17)	LaAT 1–3 SlAT 0–2 SmAT 11–18	0–4 (3)	LaAT – SlAT – SmAT 0–4
20 days	16–28 (25)	LaAT 2–4 SlAT 1–3 SmAT 14–21	10–16 (12)	LaAT 1–4 SlAT 0–3 SmAT 6–12	0–5 (2)	LaAT – SlAT – SmAT 0–5
50 day	17–31 (22)	LaAT 2–4 SlAT 1–3 SmAT 15–25	9–15 (11)	LaAT 1–3 SlAT 1–2 SmAT 7–14	0–3 (2)	LaAT – SlAT – SmAT 0–3
Adult	14–27 (18)	LaAT 3–5 SlAT 1–3 SmAT 10–22	11–19 (13)	LaAT 1–3 SlAT 0–2 SmAT 8–16	0–3 (2)	LaAT – SlAT – SmAT 0–3

ttachement plaques were less frequent on the large terminals which synapsed in the plane of section, and they lso occasionally occurred in large endings which seemed to lack synaptic junction.

Slender axon terminals making synapses on the cell bodies were not seen on the cell perikarya t this age.

The small axon terminals aried in both length and diameter from 0.2–1.0 μ. The length of their cti zone was bout the same as the length of the ending, and the shape was somewh t convex toward the cytomembrane. These terminals contained exclusively an abundance of agranular synaptic esicles. No other presynaptic organelles were observed.

Axo-dendritic synapses

The number f synaptic contacts between the proximal parts of the dendrites and the surrounding axon terminals of various sizes was great (Fig. 4). On the distal parts of the dendrites similar contacts occurred in lesser number although they were more numerous than on the cell bodies. The synaptic population on the proximal parts of the dendrites per unit length of the cytomembrane was 3 to 4-fold that seen on the giant cells. Calculated on the total available material the same number and types of



Fig 3 — Electron micrograph showing a medium-sized neuron in Deiters nucleus of a newborn rat. Light glial cell is in typical satellite position to the neuron, although separated from it by axon terminals. Arrow points to stacks of endoplasmic reticulum cisternae in the cytoplasm of the neuron. × 8000

synapsing on a giant cell figure varied from 4–7. The majority of these terminals were large (Table I).

The number of synapsing terminals per medium sized neuron figure varied from 2–4. Large nerve endings were most frequent.

The small neurons were exclusively covered by small axon terminals. Of these, only a very small proportion synapsed on the cell figure in the plane of section. No *synapses were established on the majority of the small neurons.*

The large axon terminals measured 1–2.5 μ in length and 0.5–1.0 μ in diameter. Agranular synaptic vesicles occurred in the neighbourhood of the synaptic zones though relatively sparsely. They were spherical and varied in size from 500–700 Å. Granular (= large dense core) vesicles measuring 800–1 500 Å were seen in about half of the large terminals per section, varying in number from 1–3. The majority of the large terminals contained one small mitochondrion. Both neurofilaments and microtubules occurred in relative abundance. The large axon terminals usually each contained one "active" junctional zone, sometimes two. *Desmosomal junctions or*

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The small neurons were exclusively covered by small axon terminals. Of these only a very small proportion synapsed on the cell figure in the plane of section. No synapses were established on the majority of the small neurons.

The large axon terminals measured 1–2.5 μ in length and 0.5–1.0 μ in diameter. Agranular synaptic vesicles occurred in the neighbourhood of the synaptic zones, though relatively sparsely. They were spherical and varied in size from 300–700 Å. Granular (= large dense core) vesicles measuring 900–1 500 Å were seen in about half of the large terminal per section varying in number from 1–3. The majority of the large terminals contained one small mitochondrion. Both neurofilaments and microtubules occurred in relative abundance. The large axon terminals usually each contained one "active" junctional zone, sometimes two. Desmosomal junctions or



Fig. 5. – Electron micrograph of the neuropil in the lateral vestibular nucleus of new born rat. Numerous axo-axonal contacts are formed (arrows). Also part of [illegible] light glial cell is seen. × 16000

NEUROGLIA

Dark glial cells constituted 60–70 per cent of the glial cell population. Their ovoid or elongated nuclei stained heavily with toluidine blue. Sometimes their cytoplasm also appeared either partly or entirely dark stained.

The size of this smaller type of glial cells (Fig. 2) varied from 5–7 μ. Both the nucleus and the cytoplasm stained more heavily than in the light cells. The cell organelles – small mitochondria, sometimes nicely arrayed rough endoplasmic reticulum tubules and Golgi apparatuses – were distinctly seen in the scanty cytoplasm. In addition to clusters of ribosomes, the cytoplasm contained uniformly distributed granular material, which gave these cells their typical dark appearance. In general, these cells were more distantly located in the neuropil, and they were only occasionally seen close to neurons (Fig. 2).

The cytoplasm of the light glial cells did not stain with toluidine blue. Compared with the dark glial cells, their nuclei stained much more lightly and were definitely larger. The nucleus seemed pear-shaped or polygonal and always gave a general impression of clumsiness. In the light microscope the majority of these cells were satellites of neurons, and the cells which were not apposed to neurons were located

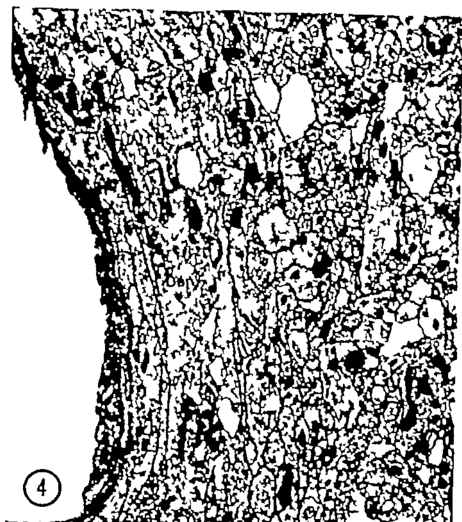


Fig. 4. — Electron microscopic view of the neuropil in the lateral vestibular nucleus of a newborn rat. To the left, the proximal part of a dendrite of a medium sized neuron is seen in longitudinal section. Axon terminals of various sizes (thick arrows) synapse on the right margin of the dendrite. × 8000.

synapsing axon terminals were seen on the dendrites originating from all neurons. Terminals of both of the two slender types also occurred. The axon terminals were morphologically similar to the axo-somatic terminals, but all types of nerve endings, the small ones in particular synapsed more frequently on the dendrites than on the cell body. Synapses were often established on the regularly occurring dendritic thorns. There were sometimes 3—4 synaptic contacts per one dendritic thorn.

Axo-axonal synapses

Axo-axonal synapses were most numerous more distantly in the neuropil (Fig. 5) where they were a constant finding. The synaptic contact was always between two adjacent relatively large axons. The extent of the synaptic zone varied from 0.3—0.8 μ; its length was determined by the size of the synapsing axon terminal. Axon terminal of various sizes or axons by passage occasionally synapsed on large axon terminals, which in turn were in synaptic contact with neuronal perikarya or dendrites. Moreover small terminals synapsed on the axon hillock of giant neurons.



Fig. 1. — Electron micrograph of the neuropil in the lateral vestibular nucleus of newborn rat. Numerous axo-axonal contacts are formed (arrow). Above, part of a light glial cell is seen. × 16000.

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near groups of neurons. In contrast to the dark glial cells, these light cells were only occasionally seen more distantly in the neuropil.

The glial cell figures of this larger type varied *in size from 6–10 μ. Both the relatively* large lobulated nuclei and the cytoplasm of these cells stained more weakly and the details of the organelles were less distinct than in the smaller type of glial cells. The cytoplasm contained a varying number of electron dense granules, which occasionally formed groups of considerable size. The structures best distinguished in the cytoplasm were fairly large mitochondria, smooth in appearance, short rough endoplasmic reticulum tubules *and vesicles of various sizes. The cytoplasm frequently* sent out variously shaped processes into the surrounding neuropil and the contour of the cytoplasm was sometimes indistinct. The light glial cells were satellites of neurons also as seen in the electron microscope. This relation was often so marked that either their body or a broad process was immediately apposed to the neuronal cell body. Mostly, however, they were separated from the neuron by axon terminals (Fig. 3).

Four Day Old Rats

GENERAL FEATURES

The abundance and variation of the total cell population attracted attention. The neuropil was heterogeneous and displayed topographical variations (Fig. 6). Giant and medium sized neurons were most numerous in the dorsocaudal part of the nucleus; in the rostroventral part they occurred in considerably lesser number. The disposition of the neurons into groups of 3–5 was also more distinctive in the dorsocaudal part. The details in the neuropil were more easily distinguished than before. The most striking observation, however, was the appearance of a new type of cell. These "new cells" (Figs. 6, 13 a *and* b) *not identifiable in the light microscope* as either neurons or glial cells, occurred in abundance in the neuropil. They were spheroid or elongated and had a very large nucleus, surrounded by a narrow rim of heavily stained cytoplasm. The size was about the same as that of the glial cells and small neurons. The size of these cells varied greatly and they were most numerous in the dorsal part of the nucleus. Moreover, uniformly distributed glial cells of dark and light types occurred in abundance.

Bundles of nerve fibres and dendrites originating from neurons were clearly distinguished. *Capillaries of small calibre* were numerous. Early myelination figures in the ventral part of the nucleus were another noteworthy feature. The fibres arriving with the vestibular nerve seemed to be most strongly myelinated. Myelinated fibres were occasionally encountered in the central part of the nucleus, but the dorsal part was free of them. In the electron microscope most of the nerve fibres of various *calibres could be identified as unmyelinated axons coursing in various directions.* Axons with a very thin myelin sheath could be seen especially in the fibres of large calibre (1–2.5 μ). Axo-axonal synapses consisting of small axons synapsing on one another or on larger axons were common. A considerable proportion of the neuropil was taken up by various glial cells, which generally sent off large and clumsy processes.

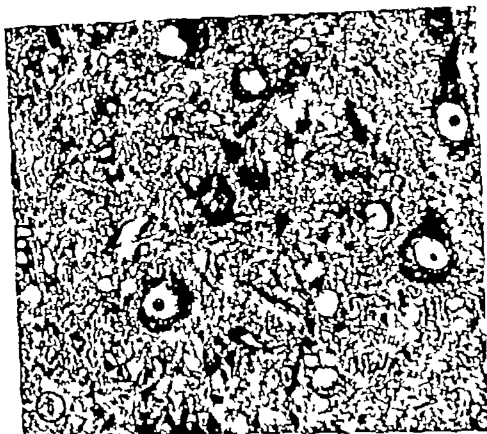


Fig. 6 – Light micrograph of the rostral part of the lateral vestibular nucleus f 4-d y ld rat. Nissl substance is unevenly distributed in the cytoplasm f giant neurons. Large lumps of Nissl substance and pale vacuoles re seen. I the cytoplasm of medium-sized and small neurons the Nissl substance is scanty. Not the great number f new glial cells (double small arrows) in the neuropil. Some myelinated fibres re also seen. Toluidine blue stained Epon-Araldite section. × 400

NEURONS

The nuclei f all types of neuron showed no changes in size or shape compared to the previous tage but the giant and medium-sized neurons had lost their perinuclear cisterns nd the cleft between the nuclear membranes was thus throughout narrow (250–500 Å). Perinuclear cisterns with many connections to the rough endoplasmic reticulum were common in th small neurons. The Nissl substance stained heavily with toluidine blue. This was true in particular for the giant cells.

I some giant neurons the Nissl substance was relati ely uniformly dispersed throughout the cytoplasm, while in others large clumps of Nissl substance were peripherally located. The staining f the cytoplasm in the medium-sized and small neurons was weak and even Nissl bodies were not clearly distinguished.

I general it was obvious that the giant cells (25–35 μ) were more pleomorphic than in the newborn rat. Multipola and spindle-shaped forms occurred in greater number tha before although spheroid and elongated cells were still most common. This may in part be due to the fact that the broad proximal parts f dendrites were

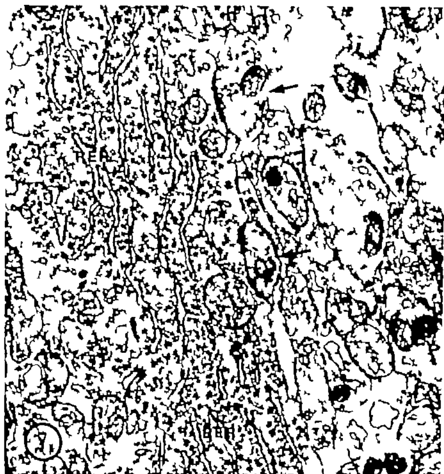


Fig. — Electron micrograph of the lateral vestibular nucleus of a 1-day-old rat. Highly organized rough endoplasmic reticulum and ribosomes are seen in the cytoplasm of giant neuron. Two small axon terminals (arrows) synapse on the cell body of the giant neuron × [illegible]0000

more conspicuous. The medium sized neurons (15—25 μ) were invariably spheroid or ovoid and showed uniformly distributed cytoplasm. By contrast, the cytoplasm of the small neurons (5—15 μ) was still scanty.

As a rule, the amount of rough endoplasmic reticulum and the number of ribosomes increased markedly with increasing size of the neurons. However, there were considerable differences in the amount and shape of the rough endoplasmic reticulum tubules present in neurons of different sizes. In some giant neurons the rough endoplasmic reticulum showed beginning organization as a separate region with parallel tubules and clustered ribosomes (Fig. 7). These regions were relatively extensive, often scattered and not always clearly demarcated and mostly located peripherally in the cytoplasm of the giant neurons. Mitochondria, neurofilaments, microtubules and numerous Golgi apparatuses were for the most part located in the cytoplasm round the nuclear membrane. In other giant neurons the distribution of the cell organelles was very variable. Sometimes the cytoplasm contained a small area with a rather primitive arrangement of the rough endoplasmic reticulum. In the small neurons the rough endoplasmic reticulum was scanty, the tubules were short and wide with numerous swellings and the ribosomes were mainly scattered all over the cytoplasm. The morphology of the medium-sized neurons (Fig. 8) resembled that

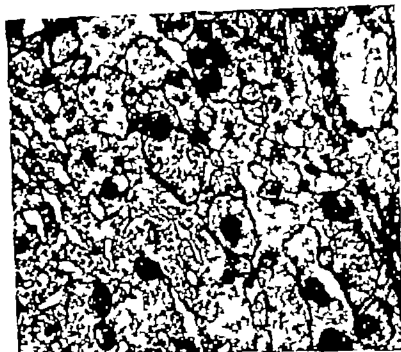


Fig. 8. — Electron micrograph showing the cytoplasm [ ] medium-sized neuron and the surrounding neuropil in the lateral vestibular nucleus [ ] 4-day-old rat. Note short and plump rough endoplasmic reticulum tubules which are not [y]et full[y] organized, although the surrounding ribosomes [a]re clearly arranged in clusters. Typical small axon terminal (thick arrow) synapses on the neuronal surface. I[n] the neuropil, a small [a]xon terminal probably synapses on another [a]xon (thin [ar]row). × 20000.

[o]f both the giant and the small neurons, especially the latter however. The rough endoplasmic reticulum tubules were mainly short and wide, although narrower and longer tubules [a]lso occurred. I[n] general, the rough endoplasmic reticulum and the ribosomes were distributed throughout the cytoplasm. In many cells, however, the endoplasmic reticulum was organized [a]t places into parallel arrays [o]f tubules, slightly primit[ive] in appearance. Ribosomes occurred mostly in clusters. Neurofilaments were present in all neurons, most numerously in the giant cells. Microtubules were occasionally observed peripherally in the cell. These structures were never [a]bundant, however.

SYNAPSES

Axo-somatic synapses

The number of synaptic [a]xon terminals, on the giant neuron, had increased to 10–25, being mostly however unde[r] 15. The majority were small endings (Table I). The large ones constituted [a]bout one-third of the total number of synaptic axon terminals on the cell per section. Most synapses to the medium-sized neurons were small, even though large terminals sometimes predominated in some neurons. Usually 5–12 synapses per section were present in the medium-sized neuron.



Fig — Electron micrograph of the lateral vestibular nucleus of a 4-day-old rat. Highly organized rough endoplasmic reticulum and ribosomes are seen in the cytoplasm of giant neuron. Two small axon terminals (arrows) synapse on the cell body of the giant neuron × 20000

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Fig. 9. – Electron micrograph showing the [illegible] on of [illegible] giant neuron in the lateral [illegible] estibular nucleus of [illegible] 4-day-old rat. The well developed endoplasmic reticulum of the giant neuron does not extend into the [illegible] on hillock. Numerous axon terminals of [illegible] arious sizes synapse on both the [illegible] on hillock (AH) and the cytomembrane of the initial segment (IS). T[illegible] light glial cells [illegible] re seen. At th[illegible] age their processes are few in number. × 8 000

All synapses on the small neurons were small The number varied from 0–5 per cell figure.

In longitudinal sections the large axon terminals measured 2.5–4 0 μ in length and 0.5–1.2 μ in diameter Their size had doubled Most synaptic vesicles were agranular but 1–2 vesicles occurred in almost half of the terminals. The majority of the large axon terminals contained 1–5 mitochondria There were usually 1–3 junctional zones per terminal. Their maximum length was 0.5 μ Desmosomal junctions, measuring 0 4—0 6 μ in length, were also seen in most large endings.

Slender axon terminals did not synapse on the cell bodies in this age group either The diameter of the small axon terminals was less than 1.5 μ usually varying between 0.5 and 1 0 μ The active zone of the small axon terminals was relatively straight, though mostly somewhat bulging with the convexity towards the cytomembrane. The small axon terminals contained numerous agranular synaptic vesicles, but 1–4 granular vesicles were also seen per section in nearly all terminals A few mitochondria could be seen in all the synapse types. Mitochondria were rare in small terminals.

Axo-dendritic synapses

The axon terminals synapsing on dendrites were identical with the axonal endings synapsing on neuronal cell bodies with regard to shape, structure and size. Synaptic slender terminals of both types were also regularly seen. The type of axon terminal synapsing on a dendrite bore no relationship to the size of the neuron from which the dendrite originated both large and slender terminals also synapsed on the dendrites originating from small neurons However most numerous were the synaptic axon terminals on the proximal parts of the dendrites given off by giant cells. On the other hand small terminals also predominated on the main stem dendrites in roughly the same proportion as on the cell perikarya

The ratio of axo-dendritic to axo-somatic synapses calculated per unit length of the cytomembrane had decreased apparently owing to the increased number of the latter There was no noteworthy rise in number of axo-dendritic synapses. These were about twice as numerous as the axo-somatic synapses, calculated per unit length of the cytomembrane. Small axon terminals surrounded numerous dendrites.

Axo-axonal synapses

The axons of various sizes crossing each other more distantly in the neuropil frequently formed synaptic interconnections. Both small and large axons made numerous synaptic contacts. The length of the synaptic zones varied from 0 5—1 0 μ

Small axons, close to neuronal cell bodies, also synapsed on preterminal large axon terminals These synapses differed from the above-mentioned ones only with regard to their shorter synaptic zone

The axo-axonal synapses on the axon hillock region formed a separate group The axon hillock and initial segment of a giant cell were surrounded by the same kind of axon terminals with regard to shape size and content as the remainder of the cytomembrane (Fig 9) Most of them were small but some could be classified as

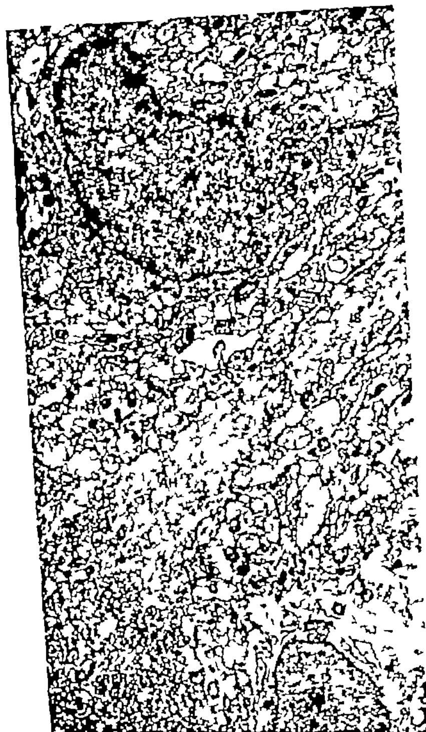


Fig. 9 – Electron micrograph showing the axon of giant neuron in the lateral vestibular nucleus of 4-day-old rat. The well developed endoplasmic reticulum of the giant neuron does not extend into the axon hillock. Numerous axon terminals of various sizes synapse on both the axon hillock (AH) and the cytomembrane of the initial segment (IS). The light glial cells are seen. At this age their processes are few in number. × 8 000

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In longitudinal sections the large axon terminals measured 2.5—1.0 μ in length and 0.5—1.2 μ in diameter. Their size had doubled. Most synaptic vesicles were agranular but 1—2 vesicles occurred in almost half of the terminals. The majority of the large axon terminals contained 1—3 mitochondria. There were usually 1—3 junctional zones per terminal. Their maximum length was 0.5 μ. Desmosomal junctions, measuring 0.4—0.6 μ in length, were also seen in most large endings.

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Fig. 11. — Electron micrograph of the lateral vestibular nucleus of a 4-day-old rat. A dark glial cell of the oligodendrocytic line is seen close to a giant neuron, although separated from it by a process coming from a neighbouring dark glial cell. × 8 000

even darker than the nucleus and contained an abundance of filled rough endoplasmic reticulum tubules, Golgi membranes, free ribosomes or polyribosomes, sharply defined mitochondria and numerous Golgi cisterns. The other type of dark glial cell (Fig. 11) resembled the former to a considerable degree. In some of these cells the nucleus was even darker than the cytoplasm and often triangular in shape. These nuclei were very rich in chromatin, often containing chromatin clumps. A common feature of both these cells was that they very rarely sent out short processes.

Generally only the moderately staining nuclei of the light glial cells were identified in the light microscope. They were mostly ovoid or pea-shaped, lobulated, relatively broad and had an eccentric, hardly distinguishable nucleolus (Fig. 6). The surface area of the nucleus alone was usually larger than the area of the majority of the dark glial cells. The light glial cells were often located close to neurons and were more numerous than before.

On the fine structural level the light glial cells (Fig. 12) were all very like each other. They differed mainly with regard to shape and size (6–15 μ). The nuclear chromatin was scanty and uniformly distributed. The eccentric nucleolus was indistinct in outline. The cytoplasm, which was mostly rather scanty, contained only few organelles. The rough endoplasmic reticulum and free ribosomes, sometimes forming clusters, were seen. The mitochondria were large and smooth in appearance



Fig 10 — Electron microscopic [illegible] of dark glial cell in the neuropil of the lateral vestibular nucleus of [illegible]-day-old rat *representing the highest degree of maturation seen in* cells of the oligodendrocytic line at this age. The *cytoplasm contains an abundance of* filled rough endoplasmic reticulum tubules, Golgi membranes, both clustered and free ribosomes and sharply defined mitochondria. × 8 000

large axon terminals. The synaptic zones were usually short and the endings lay close to each other. They synapsed on both the axon hillock and the initial segment. They contained only a few cell organelles; their main content consisted of agranular synaptic vesicles, even if a few granular synaptic vesicles were present.

NEUROGLIA

The dark glial cells were readily distinguished. The dark staining nucleus was spherical or elongated and had a clearly discernible, centrally placed dark nucleolus (Fig. 6). *The cytoplasm was very abundant and stained intensively with toluidine blue.* Numerous single cells occurred everywhere in the neuropil but groups of 5—[illegible] were also seen.

The size of the dark glial cells varied from 5—15 μ. These cells were of two different types and had a heavily staining cytoplasm. They had an almost spherical nucleus, containing relatively abundant, uniformly dispersed chromatin, which lined the nuclear membrane as a denser band (Fig. 10). The cytoplasm was sometimes





Fig 1 — Electron micrograph showing a typical light glial cell in the lateral vestibular nucleus of a 14-day-old rat. Just as most other cells of the astrocytic line it represents a considerable degree of maturity in contrast to the new glial cells appearing in the nucleus at the same time. The content of cell organelles is scanty and the mitochondria are large and smooth in appearance × 8 000

and occurred sparsely Vesicles of various sizes were numerous. They had numerous slender cytoplasmic processes extending into the surrounding neuropil.

The new cells, measuring 5—11 μ in diameter were also observed in the light microscope. Their ultrastructural features as seen in the electron microscope were similar to those of the light glial cells (Fig 13 a and b) except that the cytoplasmic processes of the new cells were clearly smaller and fewer in number

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Fig 13 — Light micrograph of the lateral vestibular nucleus of a 14-day-old rat showing giant cell surrounded by glial cells of various types, including new glial cells pointed by double arrow. Toluidine blue stained Epon-Araldite section × 320
Figs a and b represent semithin and ultrathin sections respectively adjacent to each other
Fig 13 b — General electron micrograph of the lateral vestibular nucleus of 14-day-old rat showing giant neuron and four new light glial cells in the surrounding neuropil. The nerve endings covering the giant neuron are very few and only a few of the endings synapse. The rough endoplasmic reticulum is not yet abundant and only partly organized. The cytoplasm of the new glial cells of the astrocytic line is scanty but the nucleus and the cytoplasm otherwise resemble the mature astrocytic cells seen at the same age × 1 330


15
13



Fig 12 — Electron micrograph showing a typical light glial cell in the l teral vestibular ucleus f a 4-day-old rat Just as most oth cells of the astrocytic l ne it represents consid rable d gree of m turity m contrast to the new gl al cell ppearing n the nu let t the same tim The content of cell gan lles is scanty and th m tochondri re larg and smooth n appearance × 8 000

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F g 13 a — Light m rograph f tl l t ral est b l r ucleous f 1-d y-old rat sl ow g giant cell surro unded by gl al cell f no types, nclud ng new gli l cells, pointed b d upl rrow T lu d bl e t ined Epo Arald t section × 520 Figs and b represe t a semitl n and n ultrath sect in respect ly djacent t eacl tl er

Fig 13 b — Gen ral lectron m rographic view f tl l teral est bu la n clens f 1-d ld rat, sl ow g gi nt neuron d fo new l gl t gl al cell in tl surrou d g neu rop l The n rv end g co ring f the giant neuro is rv bund nt but only a few f tl endings y apse Th rougl endopl sm ret l m n t ers bund t nd t is onl part rgan ed The cyt plasm f the new gl l cell f th astrocyt l ne is sca ty b t the lei a d tl cytoplasm th rwise resembl th t re strocytic cell seen t the same gi 6330

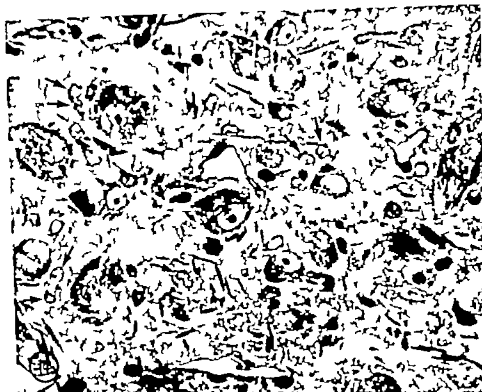


Fig. 14. – Light micrograph of the rostroventral part of the lateral vestibular nucleus of 7-day-old rat. Nissl bodies uniformly dispersed in the cytoplasm of giant neurons are clearly seen. The Nissl substance is abundant in the larger neurons, and in the giant neurons it also extends into the large nuclear indentations. Numerous glial cells are seen in the neuropil. The cells of the oligodendrocytic (small arrows) and astrocytic lines (big arrows) differ more clearly than before. Myelinated nerve fibres are also generally seen in this part of the nucleus. Toluidine blue stained Epon-Araldite section. × 400.

SYNAPSES

Axo-somatic synapses

The number of synapses per giant cell figure had increased to 21–30. Especially the amount of small synapses had increased to over two thirds of the total. The appearance of slender terminals contributed to the total increase. Large synapses were about twice as numerous as the slender ones, numbering 3–5 (Table I).

The total number of synapses on the medium-sized neurons was 10–16. Small synapses predominated (about 10) and the number of large terminals was under 5 per cell figure. Moreover 1 or 2 slender terminals could be seen.

Seven Day Old Rats

GENERAL FEATURES

The total cell population was relatively high, mainly owing to the abundance of glial cells (Fig 14) The various glial cells were located close to the neuronal soma, but they also occurred in more distant areas of the neuropil where they had a tendency to form groups of a few cells. All the different cells were advanced in differentiation they had a more mature appearance and the morphological details were more clearly discernible Both the dark and light glial cells were about equally numerous Myelination had also advanced throughout the lateral vestibular nucleus partially or fully myelinated thick axons were encountered everywhere. Som of these axons were of medium calibre (0.5—1.5 μ) Most of the neuropil was occupied by unmyelinated nerve fibres of various sizes. A relatively small proportion of the fibres were myelinated axons, occurring in all parts of the lateral vestibular nucleus and coursing in all directions. The number of small capillaries had increased.

NEURONS

The size and shape of the nuclei were the same as at previous stages except that in the giant neurons, in particular nuclear indentations were very numerous and extensive, reaching often as far as the nucleolus and containing cell organelles in greater number than previously The Nissl bodies appeared distinctively stained and evenly dispersed throughout the cytoplasm particularly in the giant and medium sized neurons. For the first time the Nissl substance appeared to be well organized. Centrally Nissl bodies occurred in the largest of the nuclear indentations. In the smaller neurons the amount and dispersion of the Nissl substance were considerably more variable. The division of the neurons into three groups was clearer than before because of a further increase in size of the largest neurons. The fine structure of the giant (25—40 μ) and medium sized (15—30 μ) neurons was more similar than in foregoing age groups. The fine structural examination revealed that the rough endoplasmic tubules with clusters of ribosomes were fully organized with an adult appearance of parallel cisterns. These areas were uniformly distributed throughout the cytoplasm in both the giant (Fig 15) and medium-sized neurons. Between the well organized cisterns there were neurofilaments and microtubules. In the giant neurons these areas sometimes lined the peripheral cytoplasm as a narrow band Other cell organelles, such as mitochondria and Golgi membranes with occasional granular vesicles (Fig 16) were concentrated in the zones occupied by neuroplasmic filaments. Microtubules also occurred in relative abundance in the same area The mitochondria were numerous smooth in appearance and varied from 0.4—2.5 μ in length and from 0.3—0.5 μ in diameter Both mitochondria and neurofilaments were most numerous in the giant and medium-sized neurons. Thorns were frequent on the cytomembranes of the giant neurons and the proximal parts of the dendrites. Glycogen granules, lysosomes, cytoplasmic inclusions or cilia were not seen. The cytoplasm was still primitive in appearance in the small neurons.



Fig. 14. – Light micrograph of the rostroventral part of the lateral vestibular nucleus of 7-day-old rat. Nissl bodies uniformly dispersed in the cytoplasm of giant neurons are clearly seen. The Nissl substance is abundant in the larger neurons, and in the giant neurons it also extends into the large nuclear indentations. Numerous glial cells are seen in the neuropil. The cells of the oligodendrocytic (small arrow) and astrocytic lines (big arrow) differ more clearly than before. Myelinated nerve fibres are also generally seen in this part of the nucleus. Toluidine blue stained Epon-Araldite section. × 400.

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Seven-Day Old Rats

GENERAL FEATURES

The total cell population was relatively high mainly owing to the abundance of glial cells (Fig 14) The various glial cells were located close to the neuronal soma, but they also occurred in more distant areas of the neuropil where they had a tendency to form groups of a few cells. All the different cells were advanced in differentiation they had a more mature appearance and the morphological details were more clearly discernible. Both the dark and light *glial cells* were about equally numerous. Myelination had also advanced throughout the lateral vestibular nucleus partially or fully myelinated thick axons were encountered everywhere. Some of these *axons* were of medium calibre (0 5–1.5 μ) Most of the neuropil was occupied by unmyelinated nerve fibres of various sizes. A relatively small proportion of the fibres were myelinated axons, occurring in all parts of the lateral vestibular nucleus and coursing in all directions The number of small capillaries had increased.

NEURONS

The size and shape of the nuclei were the same as at previous stages except that in the giant neurons, in particular nuclear indentations were very numerous and extensive reaching often as far as the nucleolus and containing cell organelles in greater number than previously The Nissl bodies appeared distinctively stained and evenly dispersed throughout the cytoplasm particularly in the giant and medium sized neurons. For the first time the Nissl substance appeared to be well organized. Centrally *Nissl bodies occurred in the largest of the nuclear indentations.* In the smaller neurons the amount and dispersion of the Nissl substance were considerably more variable. The division of the neurons into three groups was clearer than before because of a further increase in size of the largest neurons. *The fine structure of the* giant (25–40 μ) and medium sized (15–30 μ) neurons was more similar than in foregoing age groups. The fine structural examination revealed that the rough endoplasmic tubules with clusters of ribosomes were fully organized with an adult appearance of parallel cisterns. These areas were uniformly distributed throughout the cytoplasm in both the giant (Fig 15) and medium sized neurons. Between the well organized cisterns there were neurofilaments and microtubules. *In the giant* neurons these areas sometimes lined the peripheral cytoplasm as a narrow band Other cell organelles, such as mitochondria and Golgi membranes with occasional granular vesicles (Fig 16) were concentrated in the zones occupied by *neuroplasmic* filaments. Microtubules also occurred in relative abundance in the same areas. The mitochondria were numerous smooth in appearance and varied from 0 1–2.5 μ in length and from 0.5–0 5 μ in diameter *Both* mitochondria and *neurofilaments* were most numerous in the giant and medium-sized neurons. Thorns were frequent on the cytomembranes of the giant neurons and the proximal parts of the dendrites. Glycogen granules, lysosomes, cytoplasmic inclusions or *cilia* were *not seen* The cytoplasm was still primitive in appearance in the small neurons.

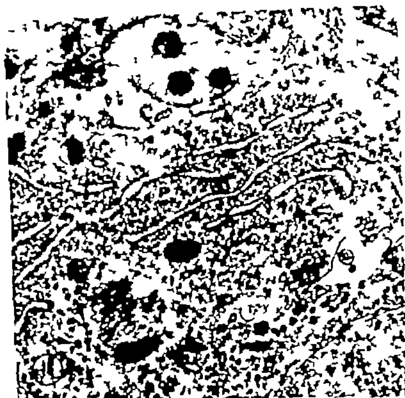


Fig 16 – Electron micrograph of the cytoplasm of medium-sized neuron in the lateral vestibular nucleus of 7-day-old rat The long arrow endoplasmic reticulum tubules with surrounding rosettes of ribosomes re well organized The Golgi apparatus is surrounded by granula esicles, marked by arrow × 20 000

Only 0–3 small synapses were seen on the small neurons.

The large axon terminals were ovoid to elongated, 5 0–6 0 μ in length and 0 8–1.5 μ in width (Fig 15). Double synapses occurred, synaptic contact being also established with an adjacent dendrite The large nerv endings were sometimes impressed into the cell body (Fig 18) The nerve endings mainly contained agranular synaptic esicles and 2–6 mitochondri Granula sy ptic vesicles were rare.

There was usually only one activ zone though 2–3 were seen in some synapses. Their length was less than 0 5 μ Desmosomal junctions were also frequent.

The lender axon terminals measured 5 0–7.5 μ in length and 0 4–0 8 μ in width. There were 3–5 active zones 0 2–0 4 μ long in these synapses Desmosomal junctions were rarely identified Agranular synaptic esicles were often seen lose to the active zones and many endings also contained 1–2 granular vesicles. Mitochondria seemed to be ery numerous.

The diameter f the small axon terminals aried from 0 6 μ – 2 5 μ and their synaptic junction was 0 4–2 0 μ The small ending was sometimes impressed into the cell body and occasionally thorn originating from the neuron was impressed into the terminal The synaptic esicles were mainly agranular but about one third of the small axon terminals lso contained 1–2 granular vesicles, and 1–2 mitochondria were frequently seen.



Fig 15 — General lectron m croscopic iew f a typical giant neuron in th l teral est b ıla nu leus of a 7-d y-old rat Th ew represent an ltratl in section adjacent t tl e semithin section sl own in F g 14 Th giant neuron w th an astrocyt in typical satell t position seen m this electron micrograpl re marked by n asterisk n F g 14 The g t neuron conta ns an b ndance f well rganized rougl endoplasmic retic lum and tt ched o free ribosomes n lusters T ghtl packed nerv endings of rıoı sizes n the neuron l cell bod generall synapse I the neuropil only axons of l rge cal bre are rro ded by my l n tion f gures 3 040

In addition some nerve endings which resembled slender terminals except that they had only one synaptic zone (1–2 μ in length) synapsed on both giant and medium ized neurons (Fig 17)

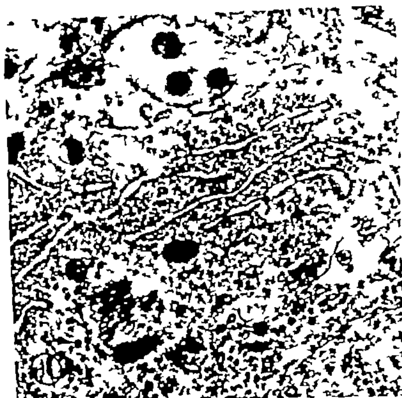


Fig 16 – Electron micrograph of the cytoplasm f medium-sized neuron in the lateral vestibular ucleus of 7-d -old rat. The long narrow endoplasmic reticulum tubules with surrounding rosettes f ribosomes are ell organized The Golgi pparatus is surrounded by granular vesicles, marked by arrows 20 000

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Fig. 15. — General electron microscopic view of a typical giant neuron in the lateral vestibular nucleus of 7-day-old rat. This view represents an ultrathin section adjacent to the semithin section shown in Fig. 14. The giant neuron with an astrocyte in typical satellite position seen in this electron micrograph are marked by an asterisk in Fig. 14. *The giant neuron contains an abundance of well organized rough endoplasmic reticulum* and attached free ribosomes in clusters. Tightly packed nerve endings of various sizes on the neuronal cell body generally synapse. In the neuropil only axons of large calibre are surrounded by myelination figures. × 5 000.

In addition, some nerve endings which resembled slender terminals except that they had only one synaptic zone (1–2 μ in length) synapsed on both giant and medium-sized neurons (Fig. 17).

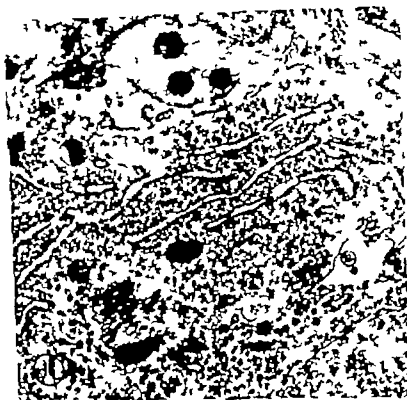


Fig. 16. — Electron micrograph of the cytoplasm of a medium-sized neuron in the lateral vestibular nucleus of a 7-day-old rat. The long, narrow endoplasmic reticulum tubules with surrounding rosettes of ribosomes are well organized. The Golgi apparatus is surrounded by granular vesicles, marked by arrow. × 20 000.

Only 0–3 small synapses were seen on the small neurons.

The large axon terminals were ovoid to elongated, 3.0–6.0 μ in length and 0.8–1.5 μ in width (Fig. 15). Double synapses occurred, synaptic contact being also established with an adjacent dendrite. The large nerve endings were sometimes impressed into the cell body (Fig. 18). The nerve endings mainly contained agranular synaptic vesicles and 2–6 mitochondria. Granular synaptic vesicles were rare.

There was usually only one active zone, though 2–3 were seen in some synapses. Their length was less than 0.5 μ. Desmosomal junctions were also frequent.

The slender axon terminals measured 5.0–7.5 μ in length and 0.4–0.8 μ in width. There were 3–5 active zones 0.2–0.4 μ long in these synapses. Desmosomal junctions were rarely identified. Agranular synaptic vesicles were often seen close to the active zones and many endings also contained 1–2 granular vesicles. Mitochondria seemed to be very numerous.

The diameter of the small axon terminals varied from 0.6 μ – 2.5 μ and their synaptic junction was 0.4–2.0 μ. The small ending was sometimes impressed into the cell body and occasionally a thorn originating from the neuron was impressed into the terminal. The synaptic vesicles were mainly agranular but about one third of the small axon terminals also contained 1–2 granular vesicles, and 1–2 mitochondria [illegible]ly seen.



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In addition, som e nerve endings which resembled slender terminals except that they had only one synaptic zone (1–2 μ in lengtl) synapsed on both giant and medium-sized neurons (Fig 17)



Fig. 13. – Electronmicrograph of the lateral estibular nucleus of 7-day-old rat, showing synapsing large terminal impressed into the cell body of giant neuron. At this age the large axon terminals contained large amount f agranular synaptic esicles. × 20 000.

NEUROGLIA

Small dark glial cells were identified by their heavily staining spherical to elongated nuclei with prominent chromatin and 1–4 nucleoli (Fig. 14). Their scanty cytoplasm w also i tensely stained. They still had tendency to occur in groups of 2–5, often in contact with each other throughout the neuropil and frequently adjacent to the capillaries.

These cells were in general considerably more alike and more mature than in the foregoing age groups, although more primitive cells also occurred. The size of the cells aried from 5–13 μ and they had only few short processes. The chromatin was relat ely uniformly distributed throughout the nucleoplasm, except close to the nuclea envelope which was lined by narrow band of condensed chromatin. The rough endoplasmic reticulum tubules and the Golgi cisterns were mostly disposed in parallel rray. Another characteristic feature was the presence of numerous clusters of ribosomes giving the cytoplasm ts dark appearance. The mitochondria were relatively sparse and small. These cells seemed t be oligodendrocytes.

The light glial cells (Fig. 15) were distinguished from the dark ones by their larger pea or kidney-shaped, often lobulated nuclei, which stained only weakly with

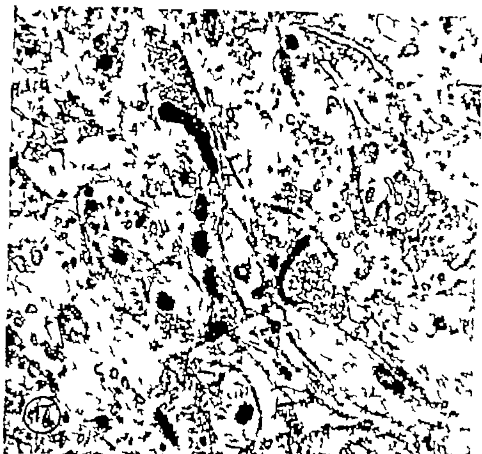


Fig. 17. — Electron micrograph showing a slender terminal with an extensive active zone synapsing on the cell body of a giant neuron in the lateral vestibular nucleus of a -day-old rat. × 20 000

Axo-dendritic synapses

A large proportion of the neuropil was occupied by mostly very extensive dendrites, given off in great number by the giant and medium-sized neurons. The synaptic junctions were similar to the axo-somatic synapses. The number of both large and slender axo-dendritic synapses on the proximal parts of dendrites was somewhat higher at this age. Some nerve endings with only one extensive "active zone" per section synapsed on both the proximal and distal parts of the dendrites. Small terminals clearly predominated on the distal parts of the dendrites, in particular.

Axo-axonal synapses

Axo-axonal synapses were most frequent between twisting axons in the distant neuropil though in lesser number than before. Their synaptic zones were similar to those of the small terminals. A small calibre axon sometimes synapsed on one or two adjacent axons. The preterminal small axon terminals adjacent to the neuronal cytomembranes synapsed more often than in the foregoing age groups.



Fig. 18. – Electronmicrograph f the lateral vestibular nucleus f 7-day-old rat, showing synapsing large terminal impressed into the cell body f a giant neuron. At this age the large axon terminals contained large amount f agranular synaptic vesicles. × 20 000.

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The light glial cells (Fig. 15) were distinguished from the dark ones by their larger pear or kidney-shaped, often lobulated nuclei, which stained only weakly with

toluidine blue. Only the nuclear membrane stained more heavily. The diameter measured 6—17 μ. These cells were not pleomorphic. They had one or two nucleoli which were lobulated and smooth in appearance. The chromatin was usually uniformly distributed, although globular chromatin aggregates were sometimes located anywhere in the nucleoplasm. The cytoplasm rarely stained heavily enough to stand out against the background in light microscopy. With the electron microscope the cytoplasm was seen sending out variously shaped thin processes between the surrounding structures. These processes contained only a few cytoplasmic organelles. The slender processes of these cells were also more abundant than before and more often extended to the vicinity of neurons, although they were only occasionally apposed to their cytomembranes. The tubules of rough endoplasmic reticulum were short and often contained floccular material. The Golgi cisterns were flat and the mitochondria long, plump and inconspicuous. Glio-filaments in parallel array were sometimes seen in the cytoplasm. The light glial cells sometimes formed groups of 2—4 and usually occurred close to neurons being satellites to them more often than the dark glial cells. These cells thus resembled astrocytes with regard to both structure and location.

Ten Day Old Rats

GENERAL FEATURES

In the light microscope the general appearance of the neuropil was very dark in tone and the various structures and their details were quite well distinguished (Fig. 19). A clear organization of the details was characteristic of the internal structure of both the neurons and the glial cells. Among the neurons the giant cells showed an increasing differentiation into a separate group as regards both size and shape. The division of the glial cells into oligodendrocytes and astrocytes had also become more pronounced. Areas were forming in the neuropil in which strongly myelinated nerve fibres predominated and other structures were infrequent. Besides myelinated axons, these areas contained unmyelinated fibres, dark glial cells and occasional small neurons. These strongly myelinated areas were surrounded by neuropil showing much less advanced myelination. This part of the neuropil contained neurons and glial cells in striking abundance, groups of 3—4 neurons in contact with one another occurred.

In the electron microscope, too, most of the neuropil was occupied by myelinated fibres varying in calibre, although the majority were thick (1.5—2.5 μ). Completely myelinated areas did not occur, even in the most heavily myelinated areas unmyelinated fibres were also relatively frequent, although they were in the minority. Myelination was more abundant than before in the immediate vicinity of neurons. Early myelination figures were considerably more common than advanced stages. As a rule the axons at an advanced stage of myelination were of large calibre and they never seemed to extend as far as the cytomembrane. However unmyelinated axons were in majority in the neighbourhood of the neuronal bodies and the proximal part



Fig. 19 — Light micrograph of the rostroventral part f the lateral estibular nucleus f 10-da -old rat. Well organized Nissl bodies are seen in the cytoplasm f giant neurons, and structural details re clearl distinguished in the smaller neurons also. Relatively mature forms occu mong both the astrocytic (big arrow) and l godendrocytic (small rrows) gl al cells. Ad anced myelination is seen in the neuropil round nerv fibres f ious calibres, but not to an appreciable extent in the neighbourhood of neurons. Toluidine blue stained Epon-Araldit section. × 400

f the dendrites. Although unmyelinated nerve fibres had become considerably less frequent, they occurred everywhere nd were usually small in calibre. A considerable stead ly increasing proportion f the neuropil surrounding the neurons was occupied by dendrites. Glial processes ry ing in shape were seen everywhere between other structures. In many places they extended as f as the cytomembranes f neurons, in other sites they continued as narrow projections insin ating themsel es between the larger xon terminals and the cytomembrane.

NEURONS

The largest of the giant neurons howed the same features that were typical f these cells t the ad lt tage. Their multipolar isodendritic nature was more obvious than before. The same characteristic features were also more accentuated in the medium sized neurons (15—30 μ).

The Nissl bodies formed rel tl ely extensive, organized, often spindle-shaped areas, separated from each other nd from the cell membrane by pale reas. This feature was conspicuous in the giant cells and also i many medium-sized neurons. In the

small neurons the cytoplasm was scanty and the details were not readily distinguished in the light microscope

The size of the neurons had remained unchanged except that a slight increase was noted in the giant cells (25–45 μ) The diameter of the small neurons varied from 10–20 μ The size shape and structure of the nuclei had remained unchanged Nuclear indentations were seen in neurons of all sizes, but they were smaller and fewer in the giant neurons than at the foregoing age.

In the electron microscope the general picture of the cytoplasm was very much the same as in the foregoing age group with regard to the number distribution and structural details of the organelles In the giant neurons extensive, well organized areas of rough endoplasmic reticulum were separated by expanding distinct areas occupied by neurofibrils and microtubules, in which the neurofilaments were disposed in parallel bundles. In many giant neurons these areas also separated the rough endoplasmic reticulum from the cytomembrane and continued into the dendrites as expanding massive zones. In the medium-sized neurons areas consisting of neurofilaments and microtubules alone were infrequent, and in the small neurons they were entirely missing

The cytoplasm of the small neurons had also changed. Rough endoplasmic reticulum tubules in parallel array were seen although the tubules were still rather short, thick and clumsy Cytoplasm primitive in appearance and lacking organization also occurred however

Mitochondria varying in length from 0.5–4 0 μ were generally found in the same areas in the cytoplasm as the neurofibrils. The mitochondria were very numerous. Subsurface cisterns occurred in the cytoplasmic membranes of the small and medium sized neurons. *Lysosomes, measuring 0 4–0 5 μ in diameter appeared for the first* time in the giant cells, usually in small groups. They were smoothly spherical in shape and the interior was dense and homogeneous. Moreover in thi age group cilia were observed for the first time on the cytomembranes of the smaller neurons. Small thorns, sometimes extending into the large terminals, were a common finding

SYNAPSES

Axo-somatic synapses

The total number of axon terminals synapsing on giant neuron figures varied from 21–34 (Table I) There were usually 4–6 large terminals and 2–3 slender ones per giant cell profile the remainder being small terminals The number of synapsing terminals per medium-sized neuron figure had risen mainly owing to an increase in small terminals. The total number of synapsing terminals per neuron profile was 14–21 Of these, only 1–3 were large Moreover 1–2 slender terminals synapsed on most medium-sized cells.

Furthermore slender terminals with an extensive active zone synapsed on some giant and medium sized neurons In the small neurons only small axon terminals occurred in a number of 0–4 per cell figure

The size of th large axon terminals varied from 3–7 μ in longitudinal sections and from 1 4–2 5 μ in diameter With regard to both size and shape the large axon terminals resembled the corresponding adult structures (Fig 20) The terminals were



Fig 20 – Electron micrograph of the lateral vestibular nucleus of 10-day-old rat, showing a typical large axon terminal between two neurons synapsing on both the giant neuron above and the perikaryonal surface of the medium-sized neuron seen below. Desmosomal junctions (arrow) are also seen between the large terminal and the neuronal cytomembrane of the giant neuron. Also typical small axon terminal synapses on the cell body of giant neuron × 20 000

to a great extent filled with granular synaptic vesicles. Mitochondria also occurred in abundance, mostly 5–6 per terminal, but even 10 per terminal were observed. Granular synaptic vesicles were infrequent. Active zones were a common finding, the average being 3–4 per terminal. They usually measured 0.3–0.4 μ in length. Desmosomal junctions, measuring 0.4–0.6 μ in length, were seen (1–3) in most of the large terminals.

The slender axon terminals varied from 4–10 μ in length and from 0.4–1.5 μ in diameter. Although the diameter seldom exceeded 1 μ. There were 3–9 active zones per terminal profile varying in length from 0.4–0.8 μ (Fig 21). Desmosomal junctions were rare. The slender axon terminals very often synapsed on surrounding dendrites. They contained abundant mitochondria, varying in number within the same range as in the large terminals. Otherwise their content was the same as in the foregoing age group. The size and content of the small axon terminals was the same as in the foregoing age group (Fig 22). The variation in shape of the synaptic zone also corresponded to the previous findings. The maximum length was 1.5 μ. The number of mitochondria sometimes rose to 5–6 per terminal profile.

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The size of the neurons had *remained unchanged* except that a slight increase was noted in the giant cells (25—45 μ) The diameter of the small neurons varied from 10—20 μ. The size, shape and structure of the nuclei had remained unchanged Nuclear indentations were seen in neurons of all sizes, but they were smaller and fewer in the giant neurons than at the foregoing age.

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Furthermore slender terminals with an extensive active zone synapsed on some giant and medium sized neurons. *In the small neurons only small axon terminals* occurred in a number of 0—4 per cell figure

The size of the large axon term nals varied from 3—7 μ in longitudinal sections and from 1 4—2 5 μ in *diameter With regard to both size and shape the large axon* terminals resembled the corresponding adult structures (Fig 20) The terminals were



Fig. 22. – Electron micrograph [of] the lateral vestibular nucleus [of] 10-day-old rat, showing three small synapsing axon terminals (thick arrows) on the cell body of giant neuron × 20 000

synapses were most ften seen in the vicinity of neurons Small axon terminals synapsed on large ones in increasing number in these sites, and the large axon termin ls in turn synapsed on the perikary f the giant and medium-sized neurons or on their dendritic main stems

NEUROGLIA

The oligodendrocytes were relatively uniform in appearance (Fig 19) in the light microscope Both the nucleus and the cytoplasm stained with toluidine blue the outlines of both were therefore distinct. The nucleus also st ined more hea ily than in any other kind f cell. Nonetheless, 1–2 nucleoli were quite conspicuous. M ny f these cells were located in myelinated reas, although they also occurred in the neigh bourhood of neurons They were single or occurred in groups of 2–5. This cell type had obviously increased in number compared with the foregoi g ge and clearly predominated among the glial cells The cell profiles f the oligodendrocytes aried in size from 5–15 μ These cells were mostly readily distinguished as separate group by the electron density of their cytoplasm, which was alw y more pronounced than in other glial cells. However there was considerable indi idual variation with regard to the general ppearance of both the ucleus and, especially the cytoplasm. The majority f these cells resembled the more mature forms described i the foregoing ge group They had an ovoid nucleus containing an abundance of chromatin, often forming clumps close to the nuclear envelope. The cytoplasm contained sparse rough endoplasmic reticulum nd numerous ribosomes, both free and in clusters. In addition, the free cytoplasm contained an bundance of fine particulate m terial, esicles f



Fig. 21. — Electron micrograph of the lateral vestibular nucleus of a 10-day-old rat. A slender terminal with numerous tiny zones synapses on the cell body of a giant neuron. A glial cell of the astrocytic type is in satellite position to the giant neuron. × 20 000

Axo-dendritic synapses

The proximal parts of the dendrites of all neurons contained various synapsing terminals in similar numbers and no morphological differences were observed between the dendrites originating from neurons of different sizes. Morphologically different terminals synapsed on the dendrites in approximately the same proportion as they did on the largest neurons although their total amount was somewhat greater on the proximal parts of the dendrites than on the cell bodies. The terminals synapsing on the main stem dendrites were mostly small. Furthermore dendritic thorns occurred in great number on the proximal parts of the dendrites. These thorns were usually in synaptic contact with many terminals; they also formed long synaptic zones when penetrating into the interior of the larger axon terminal. In addition the large and slender terminals primarily synapsing on the proximal parts of the dendrites also synapsed on one or two smaller adjacent dendrites more often than before.

Axo-axonal synapses

Axo-axonal synapses mostly distantly in the neuropil were rare. Complex axo-dendritic structures such as lateral cellular glomeruli were not encountered. Axo-axonal



Fig 21 – Light micrograph of transverse section from the dorsocaudal part f the lateral est bula ucleus f 20-day-old rat Myelin tion is abundant also in the icinity f neurons, and umerous capillaries are seen The myelinated bundles f ners f bres f large cal ber are probably cerebello-vest bular xons ntering the ucleus T l idine blue stained Epon-Arald te section × 400

tensive and in general uniformly distributed throughout the cytoplasm, except for a narrow border t the cytomembrane, which was free of them (Fig 24) Together w th Golgi membranes they also penetrated into the proximal parts f the dendrites in masses bands Parallel tubules f rough endoplasmic reticulum were more seldom seen they were mostly curved and frequently nastomosing They were surrounded by bundant rosettes mostly of 4–6 ribosomes The areas f rough endoplasmic reticulum were everywhere separated from one another by zones occupied by neurofilaments nd microt bules I the giant neurons, in particula these reas separated the Nissl bodies from the cytomembrane as narrow rim and continued as a broadening band towards the dendrites Neurofilaments generally predominated in these reas The neurof brils nd microtubules were often disposed in parallel bundles, but mostly they seemed t swirl and stream round the Nissl bodies. Golgi cisterns occurred great mber sometimes scattered over the cytoplasm, but most often located in the perinuclear rea They were alway surrounded by numerous vesicles of rious sizes nd multivesicula bodies Some f these esicles were coated, but the m jority were alveol t Large granular esicles were also common.

various sizes and bulging Golgi cisterns. The mitochondria were small and usually displayed longitudinal cristae.

In the astrocytes only the large spheroid kidney- or pear-shaped light nucleus containing one or more small nucleoli was clearly discernible (Fig. 19). The cytoplasm, which only occasionally could be identified in the light microscope, was scanty and stained weakly. With regard to size and shape these cells often resembled small neurons, although they could be identified in the light microscope owing to the fact that the neurons had a larger nucleolus and a larger and more heavily staining cytoplasm. The light glial cells were mostly located in the unmyelinated areas of the neuropil, usually close to neurons. They were satellites of neurons. In places they occurred in groups of 2—3.

The size of the astrocytes varied from 5—17 μ per cell profile. In the electron microscope they formed a very homogeneous group, greatly resembling the corresponding cells in the foregoing age group. The chromatin was usually uniformly distributed in the nucleus, which was often elongated or spherical. The cytoplasm appeared to be less lucent than previously. The rough endoplasmic reticulum tubules were long and often contained floccular material. The most conspicuous feature of the astrocytes was the great number of ribosomes, which, however, varied from cell to cell. The mitochondria were plump and long. All these cells sent out numerous, often very thin processes.

Twenty Day Old Rats

GENERAL FEATURES

The most conspicuous feature at this age was a markedly increased myelination of previously poorly myelinated areas (Fig. 25). Bundles composed of numerous, mostly thick and quite strongly myelinated axons dominated the general picture of the lateral vestibular nucleus. The smaller axons also seemed to be generally involved by the process of myelination. The neurons were often surrounded by a network of small axons at an early stage of myelination. The distribution of neurons of various sizes, their size and structural details in the light microscope did not differ appreciably from the findings in the previous age group. An abundant occurrence of small capillaries was also observed. On the fine structural level the larger axons (1.5—2.5 μ) close to neurons were also generally myelinated. The thickest of the myelinated fibres often touched the neuronal cytomembranes.

The large axon terminals were for the first time seen to originate from small myelinated axons, although this was not a frequent finding. Unmyelinated fibres occupied a relatively small proportion of the total area. They were mainly located close to neurons. The unmyelinated axons measured 0 μ in diameter.

NEURONS

The shape, size and structure of the nuclei remained the same as before. In the giant neurons (25—50 μ) the rough endoplasmic reticulum tubules were relatively inex



Fig 3 — Light micrograph f transverse section from the dorsocaudal part f the lateral estibul ucleus of 20-d y-old rat Myel ation is bundant also in the icinity f neurons, and merous capillaries re seen Th myelinated bundles f nerv f bres f large calibre re probably cerebello est bula axons entering the ucleus Toluidine blue stained Epon-Araldite section × 400

tenul e and in general uniformly di tributed throughout the cytoplasm, except for a narrow border at the cytomembrane, which was free f them (Fig. 24) Together with Golgi membranes they also penetrated into the proximal parts of the dendrites in m ss bands Parallel tubules f rough endoplasmic reticulum were more seldom seen; they were mostly curved nd frequently anastomosing They were surrounded by bundant rosettes mostly f 4—6 ribosomes The areas f rough endoplasmic reticulum were everywhere separated from one nother by zones occupied by neurofilaments and microtubules I the giant neurons, in particular these areas separated the Nissl bodies from the cytomembrane as narrow rim and continued a broadening band toward the dendrites Neurofilaments generally predominated in these reas The neurofibril d microtubules were ften disposed in parallel bundles, but mostl they seemed to sw rl nd stream round the Nissl bodies Golgi cisterns occurred in great number sometimes scattered over the cytoplasm, but most often located in the perinuclea rea They were lway surrounded by numerous vesicles of nous sizes nd multi esicular bodies Some of these vesicles were coated, but the m jority were sl ool t Large granula esicles were also common

various sizes and bulging Golgi cisterns. The mitochondria were small and usually displayed longitudinal cristae.

In the astrocytes only the large spheroid kidney or pear shaped light nucleus containing one or more small nucleoli was clearly discernible (Fig 19) The cytoplasm, which only occasionally could be identified in the light microscope was scanty and stained weakly With regard to size and shape these cells often resembled *small neurons, although they could be identified in the light microscope* owing to the fact that the neurons had a larger nucleolus and a larger and more heavily *staining cytoplasm. The light glial cells were mostly located in the unmyelinated* areas of the neuropil, usually close to neurons. They were satellites of neurons. In places they occurred in groups of 2—5

The size of the astrocytes varied from 5—17 μ per cell profile In the electron microscope they formed a very homogeneous group greatly resembling the corresponding cells in the foregoing age group The chromatin was usually uniformly distributed in the nucleus, which was often elongated or spherical. The cytoplasm appeared to be less lucent than previously The rough endoplasmic reticulum tubules were long and often contained floccular material The most conspicuous feature of the astrocytes was the great number of ribosomes, which however varied from cell to cell The mitochondria were plump and long All these cells sent out numerous, often very thin processes.

Twenty Day Old Rats

GENERAL FEATURES

The most conspicuous feature at this age was a markedly increased myelination of previously poorly myelinated areas (Fig 23) Bundles composed of numerous, mostly thick and quite strongly myelinated axons dominated the general picture of the lateral vestibular nucleus. The smaller axons also seemed to be generally involved by the process of myelination. The neurons were often surrounded by a network of small axons at an early stage of myelination The distribution of neurons of various sizes, their size and structural details in the light microscope did not differ appreciably from the findings in the previous age group An abundant occurrence of small capillaries was also observed On the fine structural level the larger axons (1 5—2.5 μ) close to neurons were also generally myelinated The thickest of the myelinated fibres often touched the neuronal cytomembranes.

The large axon terminals were for the first time seen to originate from small myelinated axons, although this was not a frequent finding. Unmyelinated fibres occupied a relatively small proportion of the total area They were mainly located close to neurons The unmyelinated axons measured 0 5 μ in diameter

NEURONS

The shape size and structure of the nuclei remained the same as before In the giant *neurons* (25—50 μ) the rough endoplasmic reticulum tubules were relatively incr

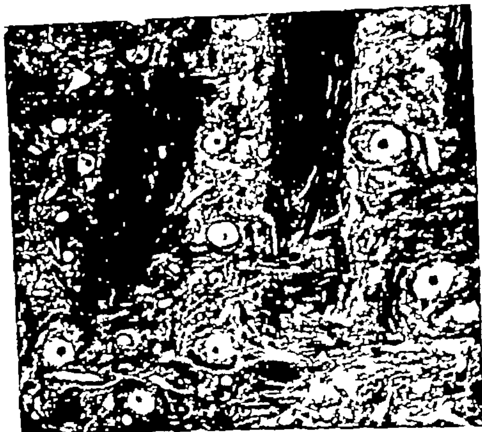


Fig. 23. – Light micrograph of transverse section from the dorsocaudal part of the lateral vestibular nucleus of a 20-day-old rat. Myelination is abundant also in the vicinity of neurons, and numerous capillaries are seen. The myelinated bundles of nerve fibres of large calibre are probably cerebello-vestibular axons entering the nucleus. Toluidine blue stained Epon-Araldite section. × 400

tenan and in general uniformly distributed throughout the cytoplasm, except for a narrow border at the cytomembrane, which was free of them (Fig. 24). Together with Golgi membranes they also penetrated into the proximal parts of the dendrites in mainly bands. Parallel tubules of rough endoplasmic reticulum were more seldom seen; they were mostly curved and frequently anastomosing. They were surrounded by abundant rosettes mostly of 4–6 ribosomes. The areas of rough endoplasmic reticulum were everywhere separated from one another by zones occupied by neurofilaments and microtubules. In the giant neurons, in particular, these areas separated the Nissl bodies from the cytomembrane as a narrow rim and continued as a broadening band towards the dendrites. Neurofilaments generally predominated in these areas. The neurofibrils and microtubules were often disposed in parallel bundles, but mostly they seemed to swirl and stream round the Nissl bodies. Golgi cisterns occurred in great number, sometimes scattered over the cytoplasm, but most often located in the perinuclear area. They were always surrounded by numerous vesicles of various sizes and multivesicular bodies. Some of these vesicles were coated, but the majority were "smooth". Large granular vesicles were also common.



Fig. 4. – General lectron m croscopic en f gi t eur Dc t rs let f 90-day-old rat Extens cytopl smic are occ pied by neuropl sm f l ment m d la ge zo es f ro gh endoplasm ret cl n d ribosomes A on term l f neu st es sy pse on th gi t neu ron My l tion f gures t d fferent t ges d xo-dendrit sy apses re see gen rall n the eu ropil × 5 680



Fig. 25 – High power electron micrograph of subsurface cistern (arrow) on the neuronal surface of giant neuron in Deiters' nucleus of 20-day-old rat. × 40 000

The mitochondria were in general uniformly distributed over the cytoplasm although they clearly avoided areas occupied by rough endoplasmic reticulum and ribosomes. They were usually small, with a maximum length of 2–5 μ. Most of the mitochondria had longitudinally oriented cristae. Lysosomes were a frequent finding in the giant neurons. Structurally they did not differ from those previously described. Stacks of several closely apposed cisterns and glia were also more common in the smaller neurons. Thorns were a regular finding and their content was the same as previously described. They were often in synaptic contact with 2–3 small axon terminals. Distinct zones mainly occupied by neurofibrils were also seen in the medium-sized neurons. In the small neurons, too, the rough endoplasmic reticulum tubules were narrower and longer than previously and to some extent topographically organized. Subsurface cisterns (Fig. 25) were regularly seen, but no cytoplasmic inclusions were encountered.

SYNAPSES

Axo-somatic synapses

The total number of synapsing terminals per giant cell profile varied from 16–28. The number of morphologically different synapsing axon terminals per neuron figure was of the same order as in the foregoing age group (Table I).

The total number of synapsing axon terminals varied from 10–16 per cross-section of medium-sized neuron, being on average nearer the former number. The distribution of morphologically different synapsing axon terminal per neuron figure was of the same order as before.



Fig. 26 a. — Electron micrograph showing a large axon terminal on the cell body of a giant neuron. Besides the usual active zone a desmosome-like junction is seen, which resembles a *gap junction. A small axonal ending is also in synaptic contact with the large axon terminal.* × 20 000.

b — Higher magnification of the junction resembling a gap junction. The close membrane apposition of this kind *usually is a sign of electrical coupling.* × 10 000.

There was no change in number of synaptic small endings per small neuron figure compared with the foregoing age groups.

Large axon terminals were similar in shape, size and contents to the corresponding structures in the foregoing age group which they also resembled with regard to synaptic zones. *The only exception was a desmosome-like junction (Fig. 26 a and b)* resembling a "gap junction" in which the opposing cell membranes converged, thus producing a narrow cleft. It measured 0.25 μ in length, and the very narrow synaptic cleft was filled with electron dense material. The size, shape and contents of the slender axon terminals were largely the same as in the foregoing age group. In general, the size, shape and contents of the small axon terminals, also were the same as in the foregoing age group. Agranular synaptic vesicles were common, occurring usually in a number of 1—5 per terminal.

Axo-dendritic synapses

There was no change compared with the foregoing age group.

Axo-axonal synapses

These synapses were mostly observed close to the neuronal cell bodies or dendrites and were most *numerous in the locations* where unmyelinated nerve fibres were in

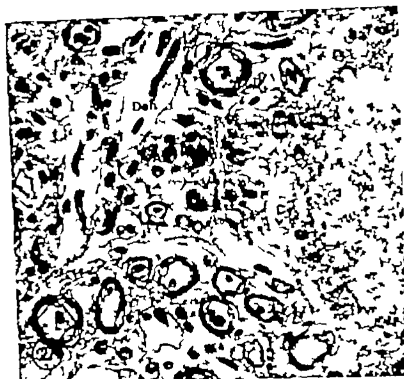


Fig 27 — Electron micrograph showing ro-axonal synapse (thick rrow) i the neighbourhood of small neuron in the neuropil in Deiters nucleus f 90-day-old rat An axon terminal synapsing on the surrounding me also synapses on adjacent dend tes (arrow heads) There are no synapsing axon terminals on the cell f the small neuron × 20 000

the majority Most axo-axonal synapses consisted of small terminals synapsing on large axon terminals, which were themselves presynapti to the neuronal cell body or the main dendritic stem Moreover adjacent axons sometimes synapsed on one another and also on adjacent dendrites (Fig 27).

NEUROGLIA

Among the glial cells oligodendrocytes were more numerous than astrocytes A considerable proportion of the f rmer were located in the areas of myelinated fibres or in groups of 5—6 close to capillaries Th astrocytes were usually situated in the vicinity f neurons, mostly single, though sometimes in groups of 2—3 The total number f glial cells seemed to be higher than before owing to an increase in the oligodendrocytes

Both broad and slender astrocytic processes insinuated themsel es in increasing numbers between the terminals into contact with the cytomembranes. The broad processes ften contained bundles of astrocytic filaments, in places lining the cytomembrane for long distances. These structures were most numerous round the large terminals, while the small terminals often lay so close to each ther on the cytomembrane that not even ery slender projections could penetrate between them.



Fig. 26 a. — Electron micrograph showing a large axon terminal on the cell body of a giant neuron. Besides the usual active zone a desmosome-like junction is seen, which resembles a gap junction. A small axonal ending is also in synaptic contact with the large axon terminal. × 20 000.
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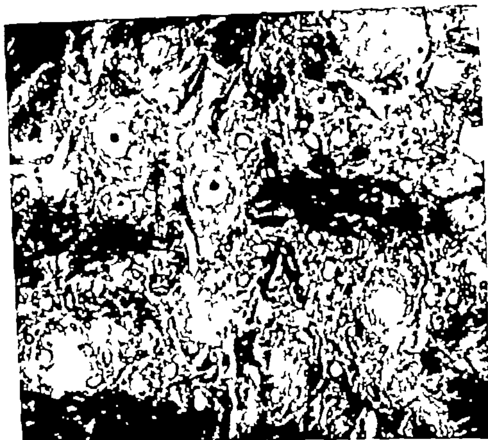


Fig 28 – Light micrograph of the dorsocaudal part f the lateral estibular nucleus f 30-day old rat Both neurons and glial cells (arrows) ha ttained adult size and represent a high degree of maturity with regard to structure The differences in size between various neurons and between neurons and glial cells are conspicuous Note also the increased myelin tion of the neuropil Toluidine blue stained Epon-Araldite section × 400

tubules were often somewhat flattened and obviously lined by fine granular material

One clearly distended axon terminal seen close to the cytomembrane f a giant cell ttracted ttention (Fig 34) It differed clearly from ther terminals by the presence f 1–2 centrally located lysosomes surrounded by large granular vesicles. In other respects t resembled the adjacent axon terminals

NEURONS

On the whole the fine structural details of the neurons resembled those seen in the foregoing age group.

The large neurons aried in size from 25–55 μ, the medium-sized neurons from 15–33 μ, and the small ones from 10–20 μ

Thirty-Day Old Rats

GENERAL FEATURES

The light *microscopic picture resembled* that seen at the foregoing age but on the other hand it did not differ *much from the adult stage* either Myelination had increased to some extent (Fig 28)

At the same time the mostly thinner fibres in the vicinity of neurons generally showed early myelination figures or were myelinated The different *categories of neurons* approached the adult stage with regard to size shape and content

No great changes were observed in the general appearance of the neuropil although the features previously described had become more accentuated In the neighbourhood of neurons early myelination figures were still very abundant round the smaller axons. Sometimes the large axon terminals synapsing on the cytomembranes of neurons originated from small axons at an early stage of myelination, but the majority obviously originated from unmyelinated axons. Myelinated axons of various sizes were very often apposed to the cytomembrane for long distances in neurons of all sizes. In the *less myelinated areas of the neuropil, synaptic complexes formed by synapsing axons* and dendrites occurred (Fig 29) resembling the lateral vestibular glomeruli.

A *very conspicuous feature was the abundant occurrence of astrocytic processes*, varying in shape in the vicinity of the cytomembranes (Fig 30) They also surrounded the axon terminals as slender projections. Dendritic expansions also appeared for the first time (Fig 29) It was typical of these structures that they were packed with mitochondria and often sent out numerous dendritic thorns. Some of the mitochondria were distorted and contained large amounts of glycogen granules. Moreover granular vesicles were regularly present in these expansions. Small axon terminals were frequently seen synapsing on them.

Axon terminals entirely deviating in structure from other terminals were also seen for the first time in this age group They occurred either in the non-*synapsing parts* of axons or synapsed on the surrounding dendrites or neurons. Mostly they appeared to be distended axon terminals, containing various unusual structures, e g abundant elongated mitochondria, the majority of which showed longitudinally oriented cristae (Fig 31) In addition, they contained granular vesicles of various sizes Bodies resembling lysosomes were also seen in these altered endings *Sometimes their axoplasm* contained fine granular material, causing a greater electron density Besides neurofilaments and agranular synaptic vesicles, *the endings contained vesicles of* various sizes.

In another type of expanded nerve ending in contact with dendrites (Fig 32) there seemed to be no or only a few synaptic vesicles adjacent to the presynaptic membrane although their structure *otherwise roughly resembled* that described above

A third type of terminal was also seen, characterized by the accumulation of tubular profiles, packed side by side and *probably parallel sometimes filling* up most of the terminal (Fig 33) The electron micrographic findings indicated that these endings could also synapse *on neurons* The altered ending seen in Fig 33 was larger than the remainder of the large terminals synapsing *on the same giant* cell. The parallel

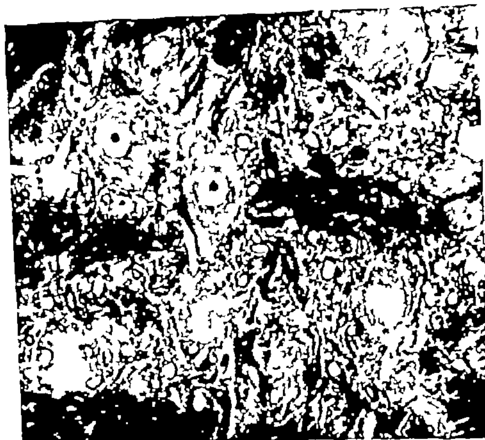


Fig 28 — Light micrograph of the dorsocaudal part of the lateral vestibular nucleus of 30-day old rat Both neurons and glial cells (arrow) have attained adult size and represent high degree of maturity with regard to structure The differences in size between various neurons and between neurons and glial cells are conspicuous Note also the increased myelination of the neuropil Toluidine blue stained Epon-Araldite section × 400

tubules were often somewhat flattened and obviously lined by a fine granular material

One clearly distended axon terminal seen close to the cytomembrane of a giant cell attracted attention (Fig 54) It differed clearly from other terminals by the presence of 1–2 centrally located lysosomes surrounded by large granular vesicles In other respects it resembled the adjacent axon terminals

NEURONS

On the whole the fine structural details of the neurons resembled those seen in the foregoing age group

The large neurons varied in size from 25–55 μ, the medium-sized neurons from 15–35 μ, and the small ones from 10–20 μ.

Thirty Day-Old Rats

GENERAL FEATURES

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At the same time the mostly thinner fibres in the vicinity of neurons generally showed early myelination figures or were myelinated. The different categories of neurons approached the adult stage with regard to size shape and content

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Fig. 30. – Electron micrograph of the lateral vestibular nucleus of a 30-day-old rat showing the cytoplasmic membrane of a medium-sized neuron, almost covered by the cell body and processes of an adjacent astrocyte. Only one synapsing small nerve ending is seen above to the left. × 40 000

The size, shape and structure of the nuclei had remained unchanged. Only nuclear indentations were rare in the giant cells.

The cytoplasm of the giant cells also contained groups of highly flattened sacs of rough endoplasmic reticulum. Such formations were previously seen only in the cyto-



F g 29 – Higl power electron n icrograpl f the europ l in the l teral est l ul uclen of a 30-day-old rat Adjacent to an astrocyt an o-dendrit ptic compl seen, whi l sm ll axon term n l (A) syn pses on th ce tral a on (CA_x), and th sm ll central axon n t m syn pses on tw adjacent dendrites Also dendrit c spa son seen probably the growing tip of the termin l segment f the dendrit on whicl one f the surrounding axons (thick rrow) synapses × 10 000



Fig 33 – Electron micrograph of the lateral ... tubular nucleus f ... day-old rat. Adjacent to the cell body of giant neuron an altered axon terminal seems to become disconnected from sy aptic contact w th the cytomembrane f the gia t cell Presynaptic membrane thickening and remnants of disintegrating synaptic vesicles (arrow) re definitely seen An aggregation of parallel t bules predominates among the contents of the degenerating terminal × 30 000

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SYNAPSES

Axo-somatic synapses

The tot l   mber f axon terminal synapsing on giant neuron figures was f the same order as   the foregoing age group. Their total n mber per giant neuron profile   ried from 17–31 (T ble I) Small terminal were clearly in the majority there were only –4 large terminal   nd 1–3 slender terminals per gi   t neuron figure.



Fig. 31. — Electron micrograph of Deiters nucleus in a 30-day-old rat. A small axon terminal synapses on the cell body of a medium-sized neuron in the vicinity of which an altered axon terminal or probably an altered preterminal axon, is seen. Besides small elongated mitochondria, the latter contains granular vesicles (small arrows) and bodies resembling lysosomes (big arrows). × 50 000.

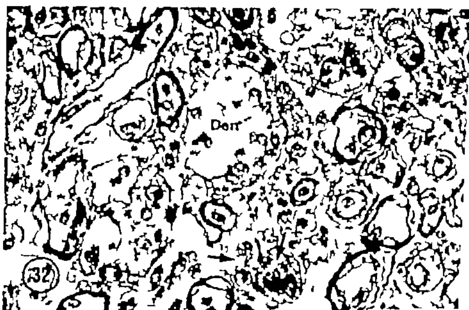


Fig. 32. — Electron micrograph of Deiters nucleus 30-day-old rat. An altered axon ending including part of an myelinated preterm l on, synapses on the surface f dendrit. Th agran la syn ptic vesicles see t disappear from the presynaptic area. Granular vesicles (small arrows) and lysosome-like bodies (big arrows) are also seen. Th the n rv ending seen on the dendritic surface n n rmal structure. × 8 000.



Fig. 33. – Electron micrograph of the lateral vestibular nucleus of a 30-day-old rat. Adjacent to the cell body of a giant neuron an altered axon terminal seems to become disconnected from synaptic contact with the cytomembrane of the giant cell. Presynaptic membrane thickening and remnants of disintegrating synaptic vesicles (arrow) are definitely seen. An aggregation of parallel tubules predominates among the contents of the degenerating terminal. ×30 000

plasm of the medium-sized and small neurons. They seemed to be flattened endoplasmic reticulum tubules containing electron dense material. They always seemed to be located in the peripheral-most cytoplasm, close to the cytomembrane. Otherwise the cytoplasm looked entirely the same as in the foregoing age group. No cytoplasmic inclusions were seen.

SYNAPSES

Axo-somatic synapses

The total number of axon terminals synapsing on giant neuron figures was of the same order as in the foregoing age group. Their total number per giant neuron profile varied from 37–51 (Table I). Small terminals were clearly in the majority; there were only 2–4 large terminals and 1–5 slender terminals per giant neuron figure.



Fig. 34 — Electron micrograph of the lateral vestibular nucleus of a 30-day-old-rat showing an altered axon terminal, or expanded preterminal part of an axon. The difference compared to other axon terminals is that two lysosomes (marked by arrow) surrounded by granular vesicles are seen at the middle of the terminal. Granular vesicles are also rare in the large endings at this age. × 90 000.

The number of synapsing axon terminals per medium-sized neuron figure was about the same as in the foregoing age group. The majority were small terminals; there were only a few large and slender terminals per cell profile. The axo-somatic synapses of the small neurons showed no change.

With regard to shape, size, content and synaptic zones the large axon terminal resembled the corresponding terminals at the foregoing age group. No change was observed in the structure of the slender axon terminal either. The small axon terminals were the same as in the foregoing age group, except that subsynaptic formations were regularly seen.

Axo-dendritic synapses

The axo-dendritic synapses resembled those seen at the foregoing age, except that 1–2 small axon terminals generally synapsed on dendritic expansions.

Axo-axonal synapses

The only difference compared with the foregoing age was that axon and dendrites in synaptic contact with one another occasionally formed synaptic complexes. Most

often the central axon synapsed only on the surrounding dendrites, while the axons surrounding the central axon were not in synaptic contact with the latter. However in one instance a peripheral axon in a lateral vestibular glomerulus was seen to synapse on the central axon (Fig. 29).

NEUROGLIA

The glial cells were readily identified as oligodendrocytes and astrocytes. The majority of the glial cells obviously represented a high degree of maturity: less differentiated, early forms were rare. The cytoplasm and sharply defined nucleoli of the oligodendrocytes stained heavily with toluidine blue. The astrocytes stained more heavily than before. The outlines of the cytoplasm of the astrocytes were often quite clearly distinguished.

The astrocytes were satellites of neurons, giant cells in particular. Oligodendrocytes were very often observed in strongly myelinated areas, and when situated close to neurons, they were most frequently seen in the vicinity of medium-sized and small neurons. The oligodendrocytes constituted about 60 per cent of the total number of glial cells, 40 per cent thus being astrocytes.

Small capillaries were abundant, especially in the less heavily myelinated areas of the neuropil. Sometimes they surrounded even single neurons in great number.

Adult Rats

GENERAL FEATURES

The neurons of various sizes were organized into groups of 3–5 per transverse section (Fig. 35). Giant cells were considerably more numerous in the dorsocaudal part of the nucleus than in other parts. Nonetheless, medium-sized and small neurons predominated everywhere in the nucleus. The dendrites of the giant cells ramified into the surrounding neuropil. The dendritic tree of the small neurons was less extensive. The shape of the giant and medium-sized neurons was more variable than that of the small neurons (Figs. 53 and 56). The former varied in shape from elongated polygons to flask- or spindle-shaped or ovoid. The small neurons were mostly spheroid or ovoid, and they had a more extensive nucleus than the larger neurons, often occupying most of the surface area in transverse sections.

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In the neuropil the process of myelination was also advanced in smaller axons close to neurons, and thus single neurons were separated from each other by myelinated fibres. Bundles of large-sized myelinated axons traversed the nucleus in all directions. Axons with incomplete myelination were also encountered, especially round the smaller axons. Both slender and small terminals sometimes originated from myelinated axons. The unmyelinated part of the neuropil was scanty and scattered, and was found by a large number of dendrites, small-sized axons and their terminals



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Small capillaries were abundant, especially in the less heavily myelinated areas of the neuropil. Sometimes they surrounded even single neurons in great number.

Adult Rats

GENERAL FEATURES

The neurons of various sizes were organized into groups f 3–5 per transverse section (*Fig.* 35) Giant cells were considerably more numerous in the dorsocaudal part of the nucleus than in other parts. Nonetheless, medium-sized and small neurons predominated everywher in the nucleus The dendrites of the giant cells ramified into the surrounding neuropil. The dendritic *tree of the small* neurons was less extensive. The shape of the giant and medium-sized *neurons* was more variable than that of the small neurons (Figs. 35 and 3?) The *former* aried in *shape from* elongated polygons t flask or spindle-shaped or ovoid *The small* neurons were mostly spheroid or ovoid, and they had more extensi e nucleus than the l rger neurons, often occupying most of the surface area in transverse sections.

In the neuropil the process of myelination was also advanced in smaller axons close to neurons, and thus single neurons were separated from each other by myelinated fibres. Bundles of large-sized myelin ted axons traversed the nucleus in all directions. Axons with incomplete myelination were also encountered, especially round the smaller axons Both slender and small terminals sometimes originated from myelinated axons. The unmyelinated part of the neuropil was scanty and scattered, nd was found by large number of *dendrites, small-sized* axons and their terminals



Fig. 35. — Light micrograph of the dorsocaudal part of the lateral vestibular nucleus of an adult rat. A typical group of neurons of various sizes, in which giant neurons predominate, is seen. Glial cells of both types (arrows) are seen in the strongly myelinated surrounding neuropil. Toluidine blue stained Epon section. × 100

and the perikarya of glial cells with their processes. There were numerous axo-dendritic and also axo-axonal synapses as well as sometimes synaptic complexes composed of axons and dendrites. These axo-dendritic complexes were so compact that astrocytic processes hardly never penetrated between them.

Dendritic expansions, mostly filled with slender elongated mitochondria, usually disposed in parallel array and containing only a few other cell organelles were seen. In addition these expansions as a rule had abundant conglomerations of glycogen granules (Fig. 40) and sometimes distorted mitochondria which also occasionally contained glycogen granules. Usually 1—2 small axon terminals synapsed on them. Axon terminals deviating markedly in structure from the remainder were also occasionally seen. They showed the same characteristic features as have already been described earlier.

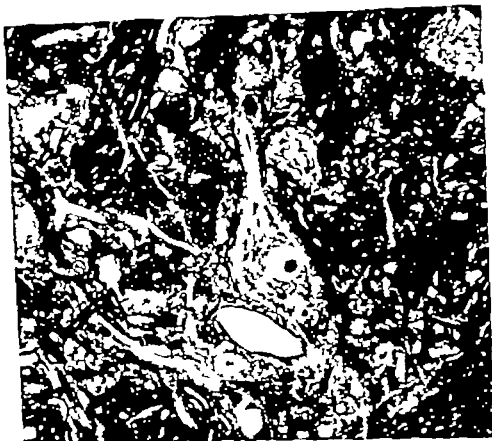


Fig 36 — Light micrograph of the rostral part of the lateral cerebellar nucleus of an adult rat, showing giant neuron typical of this part of the nucleus with regard to shape. Medium-sized neurons are most numerous in this part of the nucleus, also. Both astrocytes (big arrows) and oligodendrocytes (small arrows) are clearly distinguished. Toluidine blue stained Epon section × 400

NEURONS

I the giant and medium-sized neurons extensive Nissl bodies, readily distinguished in the perikarya, continued as massive formations even into the proximal parts of the dendrites. With decreasing neuronal size the Nissl substance became more uniformly distributed in the cytoplasm and more seldom stained as extensive bodies

Nuclear indentations were no longer seen in the giant neurons (30–55 μ); by contrast, they were common in the medium-sized (15–35 μ) and small neurons (10–20 μ). Perinuclear cisterns were seen exclusively in the small neurons, where they sometimes seemed to communicate with the rough endoplasmic reticulum tubules. The cell organelles in the cytoplasm of the giant and medium-sized neurons did not differ to any appreciable extent from those seen in the two foregoing age groups, except that peculiar inclusion bodies occurred. These inclusions, often seen in groups



Fig 35 — Light micrograpl f the d rocaudal part f th lateral estil ula nucleus f an adult rat A typical gro p of neuron of variou Izes, n which giant nei ron predomin t is seen Gli l cells of both types (arrows) are seen in the strongly myelin ted s rroun I ng neuropil Toluidine bl e stained Epon section × 400

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Dendritic expansions, mostly filled with slender elongated mitochondria usually disposed in parallel array and containing only a few other cell organelles were seen *In addition these expansions as a rul had abundant conglomerations of glycogen* granules (Fig 10) and sometimes distorted mitochondria which also occa ionally contained *glycogen granules Usu lly 1—2 n all axon terminal synapsed or tl em Axon terminals deviating markedly in str cture from the* remainder were also occasionally seen They showed the same ch racteristic features as have already been described earlier



Fig. 5 a — General electron micrographic view of the *lateral* vestibular nucleus of an adult rat showing a giant neuron with an inclusion body of fibrillar type (asterisk) centrally in the cytoplasm. The fine structure of this giant neuron is typical, and numerous typical axon terminals of various types synapse on the neuronal cell body. × 5 320

b — View of the same giant neuron in an almost adjacent semithin section. This light micrograph shows two inclusion bodies, of which only the larger one is seen in the electron micrograph. Toluidine blue stained Epon section. × 600

of 2–3 (Fig 37 a and b) consisted of fibrils twisted round each other and varied in diameter from 1–5 μ

*In light microscopic sections stained with toluidine blue these inclusions remained unstained and were thus readily distinguished They were often centrally located in the cytoplasm of giant cells. Most inclusions were round or ovoid (Fig 38) and were separated from the surrounding cytoplasm by a membrane This was for the most part single though it seemed to be double in some sites or even of a simple tubular structure There was one variety (Fig 39) with a very thick wall, mostly made up of laminated partitions varying considerably in number in different parts of the inclusion. The content consisted of the same kind of fibrils as described above but their number seemed to decrease with increasing wall thickness.

In small neurons the rough endoplasmic reticulum tubules were more uniformly scattered over the cytoplasm than before The tubules were similar in shape in neurons of different sizes, but in the small neurons they were less numerous. Neurofilaments and microtubules also occurred in the cytoplasm of small neurons.

SYNAPSES

Axo-somatic synapses

The total number of axon terminals synapsing on the giant neuron profiles was of the same order as at the foregoing age varying from 14–27 In general the largest of the giant neurons had more synapses and the majority of them were small The number of large terminals varied from 3–5 that of slender terminals from 1–3 per giant neuron figure (Table I)

There was considerable variation in the number of terminals per cell profile synapsing on medium sized neurons. The total number varied from 11–19 but the mean was nearer the first mentioned figure The majority were small terminals, 1–5 large ones and 0–2 slender terminals per medium sized neuron profile.

Both large and medium sized neurons were quite often in synaptic contact with elongated terminals with an extensive synaptic zone.

Only a few axon terminals synapsed on the small neurons. There were usually 1–3 small terminals per cell profile.

The large axon terminals were either spherical or elongated In the former case the ending appeared to be deeply impressed into the cell body Most often these terminals were spindle shaped however with a length of up to 10–12 μ and a width never exceeding 3–4 μ They often differed from the other terminals in their dark appearance which seemed to be due to their high density of agranular synaptic vesicles. They generally also contained up to 10–50 small mitochondria Granular synaptic vesicles were rare An average of 3–5 short "active zones occurred per terminal and they did not exceed 0 5 μ in length Desmosomal junctions were also seen in nearly all terminals but no gap junctions" occurred

The structure of the slender axon terminal had not changed Their length often varied from 10–15 μ while their width was usually under 1 μ "Active zones" were numerous often amounting to 10–15 per terminal Desmosomal junctions were rare Granular vesicles were seldom encountered in the slender axon terminals.



Fig. 57. — General electron micrographic [illegible] of the lateral vestibular nucleus of an adult rat showing a giant neuron with an inclusion body of fibrillar type (asterisk) centrally in the cytoplasm. The fine structure of this giant neuron is typical, and numerous typical axon terminals of various types synapse on the neuronal cell body. × 5 520

[illegible] of the same giant neuron in an almost adjacent semi-thin section. This light micrograph shows two inclusion bodies of which only the larger one is seen in the electron micrograph. Toluidine blue stained Epon section. × 600



Fig 38 — The same fibrillary inclusion as in Figs. 3 at high magnification. × 16 000.

The small axon terminals were spherical or elongated and measured from 0.5—3 μ in diameter. The synapsing side was flattened and followed the cytomembrane. Most often they had one long, sometimes two straight junctional "active zones". Quite frequently a band of electron dense material was seen beneath the postsynaptic membrane. No other junctional zones were discernible in these terminals, which contained abundant agranular synaptic vesicles. The majority of the small terminals contained some granular vesicles, though aggregations of as many as 15—20 per terminal were also occasionally seen. Just as in the other terminals, the size of these large granular vesicles varied from 800—1500 Å and the diameter of their dense core from 400—700 Å. Otherwise their structure, too, was the same as previously described.

Axo-dendritic synapses

The distribution of various kinds of synapsing endings on the dendrites resembled that seen in the foregoing age groups. Thorns were common, particularly on the proximal parts of the dendrites. They were generally smaller and narrower than on the neuronal cytomembranes.

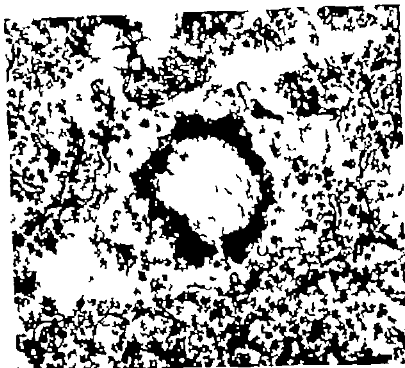


Fig. 39. – Electron micrograph showing another type of fibrillary inclusion with a multi-loculated envelope in the cytoplasm of giant neuron in the lateral vestibular nucleus of an adult rat. × 40 000

Axo-axonal synapses

Small axon terminals synapsed in great number on large terminals, which in turn were in synaptic contact with neurons or dendrites. There were sometimes 2–3 axo-axonal synapses per one presynaptic large terminal. Occasionally a large terminal synapsed not only on a neuron but also on an adjacent small axon terminal, which did not, however, seem to synapse on the neuron in question in the same plane of section. Moreover axon terminals resembling the large and small terminals on the perikaryonal or dendritic surface of neurons synapsed in larger numbers on the axon hillocks than on the initial segments of axons originating from neurons of all sizes (Figs. 41 and 42). Lateral vestibular glomeruli were more frequently seen in the neuropil than at the foregoing age. In these axo-dendritic synaptic complexes central axon frequently synapsed on the surrounding dendrites. A peripheral axon occasionally synapsed on central axon, but a contact in the opposite direction was never seen in adult animals.

NEUROGLIA

Glial cells were scattered all over the nucleus. Strongly myelinated areas were the site of predilection of the oligodendrocytes, which occasionally were also seen in groups round capillaries. When these cells were located close to neurons, the latter



Fig. 38. — The same fibrillary inclusion as in Figs. 35 at higher magnification. × 16 000.

The small axon terminals were spherical or elongated and measured from 0.5—5 μ in diameter. The synapsing side was flattened and followed the cytomembrane. Most often they had one long, sometimes two straight junctional "active zones". Quite frequently a band of electron dense material was seen beneath the postsynaptic membrane. No other junctional zones were discernible in these terminals, which contained abundant agranular synaptic vesicles. The majority of the small terminals contained some granular vesicles, though aggregations of as many as 15—20 per terminal were also occasionally seen. Just as in the other terminals, the size of these large granular vesicles varied from 800—1500 Å and the diameter of their dense core from 400—700 Å. Otherwise their structure, too, was the same as previously described.

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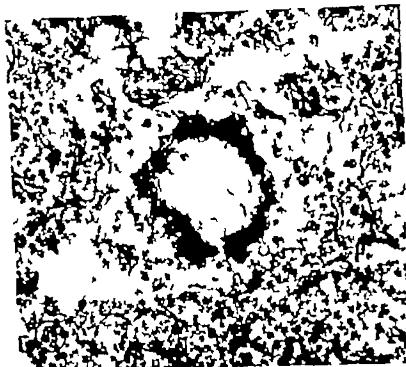


Fig. 39. – Electron micrograph showing another type of fibrillary inclusion with multilocular envelope in the cytoplasm of giant neuron in the lateral vestibular nucleus of an adult rat. × 40 000

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Small axon terminals synapsed in great number on large terminals, which in turn were in synaptic contact with neurons or dendrites. There were sometimes 2–3 axo-axonal synapses per one presynaptic large terminal. Occasionally a large terminal synapsed not only on neuron but also on an adjacent small axon terminal, which did not, however, seem to synapse on the neuron in question in the same plane of section. Moreover, axon terminals resembling the large and small terminals on the perikaryonal or dendritic surface of neurons synapsed in larger numbers on the axon hillocks than on the initial segments of axons originating from neurons of all sizes (Figs. 41 and 42). Lateral vestibular glomeruli were more frequently seen in the neuropil than at the foregoing age. In these axo-dendritic synaptic complexes central axon frequently synapsed on the surrounding dendrites. A peripheral axon occasionally synapsed on central axon, but contact in the opposite direction was never seen in adult animals.

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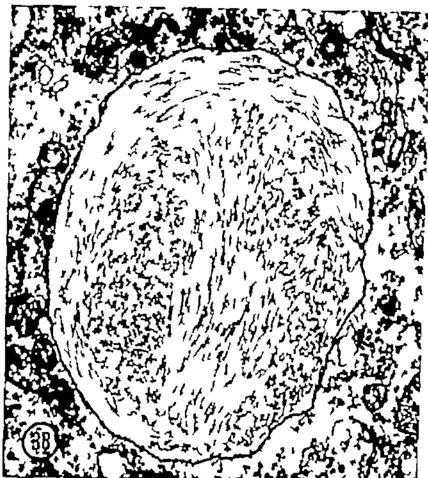


Fig 38 — Th sam e fil rillary inclusion as in Figs. 37 at higher magnif ation × 16 000

The small axon terminals were spherical or elongated and measured from 0 5—3 μ in diameter The synapsing side was flattened and followed the cytomembrane Most often they had one long sometimes two straight junctional "active zones Quite frequently a band of electron dense mat rial was seen beneath the postsynaptic membrane No other junctional zones were discernible in these terminals, which contained abundant agranular synaptic vesicles The majority of the small terminals contained some granular vesicles, though aggregations of as many as 15—20 per terminal were also occasionally seen Just as in the other terminals, the size of these large granular vesicles varied from 800—1500 Å and the diameter of their dense core from 400—700 Å Otherwise their structure, too, was the ame as previou ly described

Axo-dendritic synapses

The distribution of various kinds of synapsing endings on the dendrites resembled that seen in the foregoing age groups Th orns were common particularly on the proximal parts of the dendrites They were generally smaller an l narrower than on tl neuronal cytomembranes.



Fig 41 — Electron micrograph of the lateral vestibular nucleus of adult rat, showing an axon sent off by giant neuron. The axon hillock region (AH) and the most proximal part of the initial segment (IS) of the axon are seen. Bundles of fasciculated microtubules are visible in the cytoplasm, as well as granular material beneath the cytomembrane of the initial axonal segment. Synapsing axon terminals are more numerous on the axon hillock than on the neuronal surface of the initial segment. × 8 000



Fig 42 — Higher magnification of Fig 41. A small axon terminal is seen synapsing on the initial axonal segment, and the granular material beneath the cytomembrane of the initial segment is more clearly distinguished. × 16 000



Fig 40 — Electron micrograph of the lateral vestibular nucleus of an adult rat showing a dendritic expansion containing numerous mitochondria and glycogen granules The adjacent glial cells are oligodendrocytes. × 20 000

were usually medium-sized or small The number of oligodendrocytes per unit of surface area and their predominance among the total glial cell population had not changed, about 60—70 per cent of the glial cells being oligodendrocytes. In the light microscope they were easily distinguished from astrocytes by their heavy toluidine blue staining and the sharp demarcation of their cytoplasm and the special features of their nuclei. The poor staining and the variable shape of the nucleus and cell body facilitated the distinction of the astrocytes from the oligodendrocytes and also from small neurons even clearly in the light microscope

The size of the oligodendrocytic profiles varied from 6—15 μ Oligodendrocytes could be seen with the electron microscope to have an almost spherical to elongated nucleus with a sharply defined nucleolus eccentrically situated in the cytoplasm. The chromatin was very seldom uniformly distributed in the nucleoplasm it often formed numerous chromatin clumps peripherally aggregated along the nuclear envelope. The cytoplasm contained an abundance of ribosomes, a proportion of which was attached to the membranes of the rough endoplasmic reticulum. The tubules of the rough endoplasmic reticulum were usually short, though longer tubules were also seen, particularly round the nuclei. These tubules were always densely studded with ribosomes,

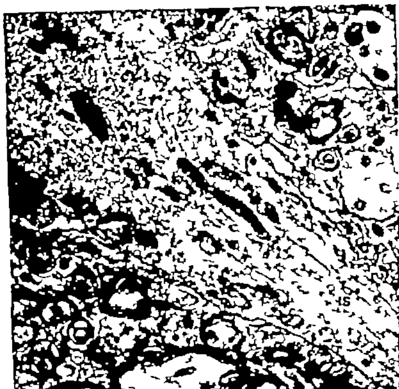


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Fig 42 — Higher magnification of Fig 41 A small axon terminal is seen napsing on the initial axonal segment, and the granular material beneath the cytomembrane of the initial segment is more clearly distinguished × 16 000

The mitochondria were prominent, being mostly small and plump though rod-shaped mitochondria also occurred The Golgi apparatus was well developed and extensive. Moreover the cytoplasm contained vesicles of various sizes, dark multivesicular bodies and at places a dense fibrillar network. When situated near a neuron the oligodendrocytes were mostly separated from the neuronal cytomembrane by myelinated fibres or dendrites, a layer of axon terminals and slender processes of the astrocytic processes. The relationship between the oligodendrocytes and the small and medium-sized neurons often seemed to be closer than before Very often the former were only separated from the latter by thin astrocytic feet, or occasionally they even seemed to be directly apposed.

The astrocytes were satellites of neurons the giant ones in particular They stained with toluidine blue more weakly than any other cells in the lateral vestibular nucleus. The diameter of the profiles of astrocytes varied from 6—16 μ The nucleus of the astrocytes was ovoid sometimes pear shaped or spheroid. The pleomorphism typical of the earlier stages had disappeared The chromatin was usually uniformly distributed over the nucleoplasm The nucleolus was smooth and eccentrically placed. The cytoplasm appeared to be very lucent owing to the sparsity of the cytoplasmic organelles. The rough endoplasmic reticulum consisted of short tubules, usually studded with ribosomes. The free ribosomes were mostly thinly scattered in clusters. The Golgi cisterns were well developed, but not numerous. The mitochondria were small and not very numerous. The most characteristic feature of the cytoplasm was the presence of bundles of filaments, which in great number seemed to penetrate into the numerous processes Moreover the cytoplasm contained variously sized vesicles, glycogen like granules and multivesicular bodies. The numerous processes branched off in increasing numbers, everywhere penetrating between the structures of the neuropil separating them from each other and from the neurons.

When the astrocytes were situated in the vicinity of neurons, giant ones in particular their extensive processes were usually in direct contact with the neuronal cytomembranes. Mostly the astrocytic cell body was separated from the neuronal cytomembrane by a zone of axon terminals. Sometimes, however the perikarya of the two cells were in direct contact with one another

DISCUSSION

NEURONAL DEVELOPMENT

The literature contains a considerable amount of data on the morphological development of nerve cells in various parts of the central nervous system (e g. Brizzee & Jacobs, 1959 Skoglund, 1969 Mellström & Skoglund, 1969 Conradi & Skoglund, 1969 a and b Altman, 1972 a, b and). Certain quantitative results on the maturation of the neurons are also available (Haltia, 1970). According to the above-mentioned and other investigations, the postnatal development of neurons varies widely in different parts f the central nervous system, reaching maturity at different times. Further more, wide variations in neuronal development have been observed even within the same parts of the central nervous system, for example between the various segments of the spinal cord (Mellström & Skoglund, 1969) and the various parts of the neocortex (Schwartz et al 1968) Furthermore, the results obtained by different authors in the same areas may not be consistent, owing in part to the use of different methods. For this reason comparison f results is difficult, as has also been pointed out previously (g Mellström & Skoglund, 1969 Haltia, 1970)

Ultrastructurally the small neurons in the lateral vestibular nucleus of the adult rat resembled th neurons of the second category in the lateral cervical nucleus of the adult cat (Westman, 1971) In both, the cell nucleus is relatively large, the endoplasmic reticulum is poorly developed, the mitochondria are few in number somatic thorns are lacking, and the axon terminal covering on the cell body is sparse. Moreover the nerv endings contacting the small neurons form a relatively homogeneous population. Neurons of small size w th similar properties have also been described in the *fascia dentata* (Blackstad & Dahl, 1962) and in the lateral geniculate body (Karlsson, 1966) f the adult rat Although the small neurons in different parts of the central nervous system have been quite extensively investigated in recent years (*e.g.* LaVelle & LaVelle, 1970 Altman, 1970, 1972 and c) the information concerning their development on the utrastructural level is relatively meagre.

Considering that the giant neurons f Deiters nucleus structurally resemble the motoneurons of the spinal cord and that numerous investigations, both morphological and quantitative, ha been performed on the latter a comparison of the development f the motoneurons and giant cells seems to be f interest.

It was shown in the present study that the giant cells of the lateral vestibular nucleus steadily increased in size throughout the first postnatal month, though most rapidly during the first 10 days. At the same time the dendritic tree became steadily

The mitochondria were prominent being mostly small and plump, though rod-shaped mitochondria also occurred. The Golgi apparatus was well developed and extensive Moreover the cytoplasm contained vesicles of various sizes, dark multivesicular bodies and at places a dense fibrillar network When situated near a neuron the oligodendrocytes were mostly separated from the neuronal cytomembrane by myelinated fibres or dendrites, a layer of axon terminals and slender processes of the astrocytic processes. The relationship between the oligodendrocytes and the small and medium-sized neurons often seemed to be closer than before. Very often the former were only separated from the latter by thin astrocytic feet or occasionally they even seemed to be directly apposed

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prenatally (Czewtyk, 1969). Concerning the development of the cytoplasmic organelles in the nerve cell cytoplasm, these observations are in agreement with previous studies even on sympathetic nerve cells (Eranko, 1972 a and b) which in adult rats are rather different from the cells of the Deiters nucleus.

In the present study the most obvious differences were observed between the fine structural development of the giant and small neurons. The changes in the structure of the small neurons were slight, the rate of change was also slow and the onset of changes was definitely later than in the giant and medium-sized neurons. Previous investigators have also reported that small cells poor in Nissl substance develop very slowly after passing the initial growth period (LaVelle 1956; Mellström & Skoglund, 1969 Altman, 1970). In the present material the small neurons attained their final nuclear and somal size during the first postnatal week, but the poorly developed rough endoplasmic reticulum and the ribosomes did not assume an appearance resembling the adult stage until the end of the first postnatal month, when they were becoming organized into small Nissl bodies. Communications between the nuclear envelope and the cisterns of rough endoplasmic reticulum, such as occurred in abundance immediately after birth also in the medium-sized neurons, were preserved in great number in the small neurons throughout the development in the cat (Mugnaini et al., 1967 b). Flattened sacs of the rough endoplasmic reticulum and subsurface cisterns previously described (Gray 1961 Rosenbluth, 1962 Mugnaini et al 1967 b Sotelo & Palay 1968) were considerably more numerous in the small neurons than in the large ones throughout the development. The role of the large number of subsurface cisterns in the small neurons, their communications between the perinuclear cisterns of the nuclear envelope, is not fully understood. It has been suggested that this system of channels may be concerned with the movements of ions or of metabolites (Rosenbluth, 1962) It has been shown that nuclear indentations and nucleotides associated with the nuclear membranes are related to the formation of cytoplasmic proteins (Hydén, 1943) In the lateral vestibular nucleus the number of nuclear indentations slowly increased in the small neurons in parallel with the development of the rough endoplasmic reticulum during the first postnatal month. The same phenomenon was also observed in the giant and medium-sized neurons during the earlier development. This is presumably a sign of intense synthetic activity in the small neurons even at the adult stage and it has been suggested that the preservation of the channel-like system and nuclear indentation in the small neurons even at the adult stage may be the morphological equivalent of this activity (Mugnaini et al 1967 b)

Since the regulation of the protein synthesis in developing mammalian nerve cells is poorly understood (Mandel & Jacob, 1970) various explanations of the rapid accumulation of the Nissl substance have been offered. Considering that cytoplasmic RNA constitutes an essential part of the protein synthetizing apparatus of the cell (de Man & Noorduyn, 1969) its marked increase postnatally obviously augments the neuronal protein synthesis (e.g. Eschner & Glees, 1963 Wechsler, 1966) It has also been assumed that the increase in the number of mitochondria as such observed in some investigations (Flexner, 1955 Richter 1967 Seiler, 1969) or in combination with enhanced energy metabolism (Seiler, 1969) is connected with accelerated RNA and protein synthesis and may also explain the observed pronounced increase in the number of mitochondria in Deiters nucleus during the early postnatal period.

more extensive, and multipolar and elongated cells increased in number Since the nucleus did not increase in size after birth, an extension of the perikaryon and its processes was involved. Similar observations have been made on the growth of motoneurons during the first postnatal month (Ngowyang 1930 Ford & Cohan, 1968) The results in question were confirmed by Mellström & Skoglund (1969) who found however that both the nucleus and cell body of the motoneurons increased in size almost exclusively during the second fortnight of postnatal life. It thus appears that in the giant cells and particularly in the medium sized neurons of the lateral vestibular nucleus, the growth period of both the nucleus and perikaryon occurred considerably earlier than in the motoneurons of the anterior horn of the spinal cord.

The population of giant neurons of the lateral vestibular nucleus appeared to follow a relatively uniform pattern of development. The changes in the nucleus were slight, similar features being observed in the nuclei of the giant neurons of both new born rats and adult animals. The nuclear indentations did, however clearly increase in size and number until the seventh postnatal day At this stage they sometimes also contained rough endoplasmic reticulum tubules, besides ribosomes, and often extended to the vicinity of the nucleolus. Subsequently the nuclear indentations gradually decreased in size and number so that none were observed in the giant neurons of the adult rat, but were still frequent findings in the medium-sized and small neurons. The rough endoplasmic reticulum and free ribosomes in the giant neurons also increased most during the first postnatal week. This was in agreement with earlier hypotheses on the association between nuclear indentitations and the formation of cytoplasmic proteins (Hydén, 1943)

An interesting change took place in the cisterns of the rough endoplasmic reticulum, which was scanty and poorly organized in the newborn. Its maturation into highly organized groups of tubules disposed in parallel array and clustering of ribosomes mainly occurred before the fourth postnatal day The organization and the quantitative increase of both the rough endoplasmic reticulum and free ribosomes were most intensive from the fourth to the seventh day continuing more slowly to the tenth postnatal day The well-developed Golgi membranes increased in number during the same period. The number of neurofilaments increased most during the first two postnatal weeks, which was later than the maturation of the endoplasmic reticulum.

The fine structural observations of the present study complement those reported in a quantitative cytochemical investigation on neuronal development in the anterior spinal horn in the rat (Haltia 1970) In this, relatively slight changes were observed in the dry mass and mean neuronal RNA content of the neurons during the first three to five days of postnatal life followed by an abrupt rise in the RNA content to the eighth day and an increase in neuronal dry mass thereafter The ratio of RNA/dry mass also appeared to rise for the first eight days of life and then remained at approximately the same level until adult age. Haltia (1970) pointed out that an intense accumulation of RNA and protein occurred mainly postnatally in the neurons in contrast to other somatic cells.

Similar results have been reported in a study on the development of the mesencephalic trigeminal neurons in the rat, in which the increase in RNA was found to be much greater and more rapid between the second and ninth postnatal days than

prenatally (Grewzyl, 1969). Concerning the development of the cytoplasmic organelles in the nerve cell cytoplasm, these observations are in agreement with previous studies even on sympathetic nerve cells (Eranko, 1972 a and b), which in adult rats are rather different from the cells of the Deiters nucleus.

In the present study the most obvious differences were observed between the fine structural development of the giant and small neurons. The changes in the structure of the small neurons were slight, the rate of change was also slow and the onset of changes was definitely later than in the giant and medium-sized neurons. Previous investigators have also reported that small cells poor in Nissl substance develop very slowly after passing the initial growth period (LaVelle, 1956; Mellström & Skoglund, 1969; Altman, 1970). In the present material the small neurons attained their final nuclear and somal size during the first postnatal week, but the poorly developed rough endoplasmic reticulum and the ribosomes did not assume an appearance resembling the adult stage until the end of the first postnatal month, when they were becoming organized into small Nissl bodies. Communications between the nuclear envelope and the cisterns of rough endoplasmic reticulum, such as occurred in abundance immediately after birth also in the medium-sized neurons, were preserved in great number in the small neurons throughout the development in the cat (Mugnaini et al., 1967 b). Flattened sacs of the rough endoplasmic reticulum and subsurface cisterns previously described (Gray, 1961; Rosenbluth, 1962; Mugnaini et al., 1967 b; Sotelo & Palay, 1968) were considerably more numerous in the small neurons than in the large ones throughout the development. The role of the large number of subsurface cisterns in the small neurons, their communications between the perinuclear cisterns of the nuclear envelope, is not fully understood. It has been suggested that this system of channels may be concerned with the movements of ions or of metabolites (Rosenbluth, 1962). It has been shown that nuclear indentations and nucleotides associated with the nuclear membranes are related to the formation of cytoplasmic proteins (Hydén, 1943). In the lateral vestibular nucleus the number of nuclear indentations slowly increased in the small neurons in parallel with the development of the rough endoplasmic reticulum during the first postnatal month. The same phenomenon was also observed in the giant and medium-sized neurons during the earlier development. This is presumably a sign of intense synthetic activity in the small neurons even at the adult stage and it has been suggested that the preservation of the channel-like system and nuclear indentation in the small neurons even at the adult stage may be the morphological equivalent of this activity (Mugnaini et al., 1967 b).

Since the regulation of the protein synthesis in developing mammalian nerve cells is poorly understood (Mandel & Jacob, 1970), various explanations of the rapid accumulation of the Nissl substance have been offered. Considering that cytoplasmic RNA constitutes an essential part of the protein synthetizing apparatus of the cell (de Man & Noordam, 1969), its marked increase postnatally obviously augments the neuronal protein synthesis (e.g. Eschner & Olsen, 1963; Wechsler, 1966). It has also been assumed that the increase in the number of mitochondria as such observed in some investigations (Flexner, 1955; Richter, 1967; Seiler, 1969) or in combination with enhanced energy metabolism (Seiler, 1969) is connected with accelerated RNA and protein synthesis and may also explain the observed pronounced increase in the number of mitochondria in Deiters' nucleus during the early postnatal period.

more extensive, and multipolar and elongated cells increased in number. Since the nucleus did not increase in size after birth, an extension of the perikaryon and its processes was involved. Similar observations have been made on the growth of motoneurons during the first postnatal month (Ngowyang 1950, Ford & Cohen, 1968). The results in question were confirmed by Mellström & Skoglund (1969) who found, however, that both the nucleus and cell body of the motoneurons increased in size almost exclusively during the second fortnight of postnatal life. It thus appears that in the giant cells and particularly in the medium sized neurons of the lateral vestibular nucleus, the growth period of both the nucleus and perikaryon occurred considerably earlier than in the motoneurons of the anterior horn of the spinal cord.

The population of giant neurons of the lateral vestibular nucleus appeared to follow a relatively uniform pattern of development. The changes in the nucleus were slight, similar features being observed in the nuclei of the giant neurons of both newborn rats and adult animals. The nuclear indentations did, however, clearly increase in size and number until the seventh postnatal day. At this stage they sometimes also contained rough endoplasmic reticulum tubules, besides ribosomes, and often extended to the vicinity of the nucleolus. Subsequently the nuclear indentations gradually decreased in size and number so that none were observed in the giant neurons of the adult rat, but were still frequent findings in the medium-sized and small neurons. The rough endoplasmic reticulum and free ribosomes in the giant neurons also increased most during the first postnatal week. This was in agreement with earlier hypotheses on the association between nuclear indentations and the formation of cytoplasmic proteins (Hydén, 1943).

An interesting change took place in the cisterns of the rough endoplasmic reticulum, which was scanty and poorly organized in the newborn. Its maturation into highly organized groups of tubules disposed in parallel array and clustering of ribosomes mainly occurred before the fourth postnatal day. The organization and the quantitative increase of both the rough endoplasmic reticulum and free ribosomes were most intensive from the fourth to the seventh day continuing more slowly to the tenth postnatal day. The well-developed Golgi membranes increased in number during the same period. The number of neurofilaments increased most during the first two postnatal weeks, which was later than the maturation of the endoplasmic reticulum.

The fine structural observations of the present study complement those reported in a quantitative cytochemical investigation on neuronal development in the anterior spinal horn in the rat (Haltia, 1970). In this, relatively slight changes were observed in the dry mass and mean neuronal RNA content of the neurons during the first three to five days of postnatal life followed by an abrupt rise in the RNA content to the eighth day and an increase in neuronal dry mass thereafter. The ratio of RNA/dry mass also appeared to rise for the first eight days of life and then remained at approximately the same level until adult age. Haltia (1970) pointed out that an intense accumulation of RNA and protein occurred mainly postnatally in the neurons in contrast to other somatic cells.

Similar results have been reported in a study on the development of the mesencephalic trigeminal neurons in the rat, in which the increase in RNA was found to be much greater and more rapid between the second and ninth postnatal days than

other cytoplasmic organelles. They were covered by only a few synapsing axon terminal. Simila structures have been described in the cerebellar cortex and hypothalamus (Ch ndler & W llis, 1966) in autonomic gangli (Sulkin et al., 1968) and in the cerebral cortex (Dahl, 1965). On the other hand it has been reported th t the first synapses of vagal f bres appe ring after deafferentation in the superior cervical ganglion were located on growing tips of dendrites (Ceccarelli, 1968). In this study similar synapses were not observed until the end of the first postnatal month, when the neuronal lement including the dendrites had passed their most intense stage f development. These expansions were lways located on the distal parts of the dendrites, which was in agreement with previous findings (Mugnaini et al 1967 b) Sotelo & P lay 1968). The question of whether they were dilations or actual terminations of dendrites cannot be nswered without investigating serial sections. Their complete absence in the early stages of development f the lateral vestibular ucleus favours the iew th t they were growing or expanding tips of changing dendrites in growing or regenerating mature nerv cell (Sotelo & Palay 1968, 1971)

In recent investigations enlarged xon terminals cont ining variety of unusual structures have been observed in the central nervous system of different animals. In general they have been considered to be due t some kind of chronic degenerative process possibly caused by nutritional deficiency or som noxious gent (see refer ences Sotelo & Palay 1971) H shimoto & Palay (1965) were the first to draw attention t the fact that nerve endings with similar inclusions are seen in the nucleus gracilis of normal adult rats and cats These uthors suggested that the altered axon terminals are the result f physiological degenerative process, starti g in early lif od continuing into maturity Similar peculiar nerve endings have since been described in the norm l cerebellum f arious animal species (Andres, 1965 Morales & Duncan, 1966 Raine & Field 1967 Hámori & Szentágothai, 1968 Hirano et al 1968, 1969 Sotelo, 1969) nd in the l teral vest bular nucleus f the adult cat (Mug naini et al 1967 b) and the adult rat (Sotelo & Palay 1971).

Similar enl rged, ltered axon terminals were observed in this study though only in the mature or nea ly mature lateral estibul r nucleus This finding favours the iew that these endings represent the degenerative phase of a cycle f degeneration nd regeneration f axon terminal in normal dults, and indicate th t axonal remodelling is process generally occurring in th mature nervous system (Sotelo & P lay 1971) Degeneration f axon terminals ought to be followed by the generation of new end gs if continuous xonal remodelling t kes place in the central nervous system So far no evidence of regenerating axon terminals has been reported The results obtained in th present study do not support th assumption f Hashimoto & Palay (1965) that axonal degeneration starts early in life.

DEVELOPMENT OF SYNAPTIC CONNECTIONS

The synaptogenesis of various parts of the central nervous system has in recent years mainly been studied in the cerebral cortex (Voeller et al 1963 Pappas & Purpura, 1964 Meller et al 1968 Adinolfi, 1971 a and b) but also in the hippocampus (Blackstad & Kjaerheim, 1961 Blackstad & Flood, 1963 Purpura & Pappas, 1968

STRUCTURES OF THE NEUROPIL

Most of the neuropil of the lateral vestibular nucleus of the newborn rat was found to be occupied by dendritic or axonal profiles of various sizes. Axonal elements predominated, because the dendritic tree of all neurons, though especially that of the small and medium sized neurons was still poorly developed as in other parts of the central nervous system (e.g. Adinolfi, 1972 Altman 1972 b) The axonal profiles were also of small calibre in the more distant neuropil, where myelinated axons of large calibre were abundant in the adult rats. Identifying axons and dendrites was often difficult during the early neonatal period, because all the axons were still unmyelinated and differences in the fine structure did not necessarily occur as previously encountered in other parts of the central nervous system (Schwartz et al., 1968) Larger axons and dendrites were more readily distinguished, because the larger dendrites often contained rough endoplasmic reticulum, mitochondria and occasional multivesicular bodies. Both axons and dendrites rapidly increased in calibre and the adult size was often attained by the end of the first postnatal week, and then it was possible to distinguish most of the axons from the dendrites.

The oligodendrocytes rapidly increased in number and myelination started round the large axons of the vestibular nerve. By the end of the first postnatal week the largest axons with early myelination figures were scattered all over the area of the lateral vestibular nucleus. These are probably fibres by passage through the lateral vestibular nucleus to the other vestibular nuclei or the cerebellum. The most intensive phase of myelination took place during the second and third postnatal weeks By the tenth postnatal day large areas of the neuropil were mainly occupied by myelinated axons of large and medium calibre, while all the axons of small calibre were unmyelinated. By the end of the third postnatal week most of the small axons, even in the close vicinity of neurons, were myelinated Myelinated axons also synapsed on the cell bodies of giant neurons, resembling the picture seen in adult animals. In agreement with previous observations (Sotelo & Palay 1968) immature myelin figures were seen round small axons even in the adults.

The development of the dendrites of all neurons was largely similar No major differences in fine structure were observed between the dendrites of the giant cells and the dendrites of the smaller cells. The dendritic tree of the giant neurons was remarkable from birth, while dendrites sent off by small neurons were not very often encountered even in sections representing the older age groups investigated. The cytoplasmic content of the small dendrites was poorer during the early postnatal period than at later stages. By contrast at the end of the first postnatal week the proximal parts of the largest dendrites of giant neurons contained tubules of rough endoplasmic reticulum and rosettes of ribosomes forming groups resembling the Nissl bodies of the adult stage Microtubules and neurofilaments were also numerous, and clusters of free ribosomes were observed even in the smallest dendritic branches. The diameter of the proximal parts of the largest dendrites doubled during the course of the postnatal development as in the motoneurons of the spinal cord (Conradi & Skoglund 1969 a)

Dendrites showing certain characteristic deviating features were encountered at later stages of development These may be described as dendritic expansions, filled with a large number of mitochondria and glycogen granules, but only few of the

other cytoplasmic organelles. They were covered by only few synapsing axon terminals. Similar structures have been described in th cerebellar cortex and hypothalamus (Chandler & Willis, 1966) in autonomic ganglia (Szilkin et al 1966) and in the cerebral cortex (Dahl, 1963). On the other hand it has been reported that the first synapses of agal f bres ppearing after deafferentation in the superior cervical ganglion were located on growing tips of dendrites (Ceccarelli, 1968). In this study similar synapses were not observed until the end of the f rst postnatal month, when the neuronal lements including the dendrites h d passed their most intense stage f development. These expansions were alw ys located on the dist l parts of the dendrites, which was in agreement with previous findings (Mugnaini et al 1967 b) Sotelo & Palay 1968). The question of whether they were dilations or actual terminations of dendrites cannot be answered without investigating serial sections. Their complete bsence in the early stages f development of the lateral vestibular nucleus f ours the iew that they were growing or expanding tips of changing dendrites in growing or regenerating matur nerv cell (Sotelo & Palay 1968, 1971).

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Simila enlarged, altered axon terminals were observed in this study though only the mature or nea ly mature lateral estibul nuclei. This f nding f vours the iew that these endings represent the degenerative phase f a cycle of degeneration and regeneration of axon terminals in normal adults, and indicate that axonal remodelling is process generally occurring in the mature nervous system (Sotelo & Palay 1971). Degeneration of axon termin ls ought to be followed by the generation of new endings if continuous axon l remodelling takes place in the central nervous system. So far no evidence of regenerating axon terminals has been reported. The results obta ned in the present study do not support the assumption of Hashimoto & Palay (1965) that axonal degeneration starts early in life.

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development, earlier in the giant neurons than in the medium-sized ones. The large axon terminals seemed to be the first to synapse on the giant and medium-sized neurons, and their number per cross-section f both giant and medium-sized neuron remained the same until the adult stage By contrast, small terminals very seldom synapsed on the perikarya of larger neurons at the newborn stage and in contrast to other endings, the two types of slender terminals synapsed on the cell bodies of giant and medium-sized neurons only at the end of the first postnatal week. The increase in the total number of synapsing axon terminals during the first postnatal week, which continued t a slower rate until the tenth postnatal day in the medium-sized neurons, in particular was mainly due to a doubling many times over of synapsing small terminals in short time To some extent it was also due to a moderate increase in both types f synapsing slender terminals in both groups f neurons The total number of synapsing xon terminals per cross-section of both giant and medium-sized neurons was found to be t its m ximum on the tenth postnatal day Subsequently the total number f synapsing nerve endings remained the same or was somewhat lower

A reduction in the number f axo-somatic synapses has lso been observed in other parts f the central nervous system In studies f the cerebellum a loss f contact between terminals and the somal surfaces f neurons during th postnatal development has been reported (Mugnaini & Forstronen, 1967 Korngoth et al., 1968), and the number of certain terminal on the cell bodies f developing spinal motoneurons decreased postnatally (Conradi & Skoglund, 1969) If the number of synapsing terminals per neuron figure really decreases in the lateral vestibula nucleus, the small endings are most l kely involved As an explanation of the loss of axon terminals t has been suggested that endings formi g double synapses leave the cell bodies and remain in contact with the neighbouring dendrites (Conradi & Skoglund 1969 a) This cannot be true for the dev loping lateral vestibular nucleus, however since small axon terminals do not form double synapses According to another theory astrocyte-like glial cells are somehow capable of removing synapsing terminals in the same way as has been found to occur on the cell bodies of regenerat ing motoneurons (Blinzinger & Kreutzberg, 1968) This explanation could also be alid for the loss of synaptic terminals possibly occurring in the giant and medium-sized neurons in Deiters nucleus, since the most intensive growth period of the astrocytic processes was bserved between the tenth and twentieth postnatal days. A regards the lateral vestibular nucleus, the most likely explanation does, however seem to be the degeneration of axon terminals observed in the present study during the later postn tal dev lopment. On the other hand, in the later age groups studied the differences in the total number of synapsing endings were too small to permit any far-reaching conclusions Moreover the material wa not very extensive, and th selection f cells f study may have distorted the results, because the number of synapsing terminals per neuron f gures ried widely in neurons of the same size and in the same age group.

Axo-dendritic synapses

In the newborn animal the total nerv ending covering was highest on the proximal parts of the dendrites in all neurons in Deiters nucleus, and until the adult stage it

Schwartz et al. 1968), in the cerebellar cortex (Konishi 1966, Larramendi & Victor 1966, Mugnaini & Forströnen 1967, Larramendi, 1967), in the spinal cord (Bodian 1966, Bunge et al. 1967, Conradi & Skoglund 1969 a and b) and in the lateral geniculate nucleus (Karlsson 1967). These studies have shown that synaptic connections develop at different times in different parts of the central nervous system, although this development generally occurs during the first few postnatal weeks in mammals. The axo-somatic synapses on the cell bodies of motoneurons in the spinal cord are well developed at birth (Conradi & Skoglund 1969 a) and synapse formation in vestibular labyrinth has recently demonstrated to occur before the birth (Heywood et al. 1975), while the corresponding structures in the cerebral cortex have not even started to develop at the birth (Voeller et al. 1963, Adinolfi 1971 b). The development of synaptic connections in the lateral vestibular nucleus of the rat as seen in the present material resembled most that of the lateral geniculate nucleus of the rat, whose fully developed neuronal connections were also seen during the first postnatal fortnight, before the animals had opened their eyelids (Karlsson 1967).

The formation of the first synaptic complexes has been accompanied by changes in the electrical activity of the tissue (Voeller et al. 1963, Purpura et al., 1965, Bunge et al. 1967, Schwartz et al. 1968). There are no discrepancies compared to the electrophysiological observations. For example, spontaneous electrical activity steadily became more regular in the cerebral cortex during the first ten postnatal days (Crain 1952) and typical cerebellar activity was recorded on the twelfth postnatal day (Jacobs & Snider 1919). No electrophysiological data on maturation of the vestibular system are available.

Axo-somatic synapses

In the present material the nerve ending covering of neurons of various sizes showed differences even in the early postnatal period. The giant neurons had the most abundant nerve ending covering, and the proportion of somal surfaces covered by terminals decreased with decreasing neuronal size, as has previously been observed in the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1970), in the lateral cervical nucleus of the adult cat (Westman 1971), in the developing motoneurons of the spinal cord (Conradi & Skoglund 1969 a) and in a three-dimensional study of two small cells in the lateral geniculate body of the adult rat (Karlsson 1966). In the present material the populations of various nerve endings on the giant and medium-sized neurons did not change during development, but slender terminals first appeared at the end of the first postnatal week on the cell bodies of giant and medium sized neuron.

Interneuronal connections were scanty at the time of birth in neurons of all sizes in the lateral vestibular nucleus, although all the neuronal surfaces were tightly packed with endings. The small neuron differed markedly from the larger ones, also with regard to the development of synaptic connection. In newborn animal the small neurons were covered by a homogeneous population of synapsing endings, consisting only of small axon terminals. These increased in number during the first few postnatal days and were still sparse at the adult stage, as previously reported in the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1970).

In the larger neurons, synaptic connections were regularly formed throughout the

development, earlier in th giant neurons than in the medium-sized ones. The large axon terminals seemed to be the first to synapse on the giant and medium-sized neurons, and their number per cross-section f both giant and medium-sized neuron remained the same until the ad lt stage. By contrast, small terminals very seldom synapsed on the perikary of l rger neurons t the newborn stage, and in contrast to other endings, the two types of slender terminals synapsed on the cell bodies of giant and medium-sized neurons only at the end of the first postnatal week. The increase in the total number of synapsing xon terminals during the first postnatal week, which continued at slower rate until the tenth postnatal day in the medium sized neurons, in particular was mainly due to a doubling many times over f synapsing small terminals in a short time T some extent it was also due to a moderate increase in both types f synapsing slender terminals in both groups of neurons. The total number f synapsing axon terminals per cross-section of both giant and medium-sized neurons was found to be t its maximum on the tenth postnatal day Subsequently the tot l number f syn psing nerv endings remained the same or was somewhat lower.

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The third kind of axo-axonal synapses were axon terminals synapsing on the axon hillock or the initial segment of an axon extending from a neuron. Criteria for the identification of both the axon hillock and the initial axonal segment in mature nervous tissue have been given by Palay et al. (1968) and the morphology and synaptology of these structures have also been described in detail in certain other reports (Peters et al. 1968, Conradi, 1969 b) including investigations of the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1968). The early stages of development of the axon hillock and initial segment have been studied even less than the mature structures (Kornguth et al., 1968, Conradi & Skoglund, 1969 b). In their three-dimensional studies of the development of the initial motoraxon segment in the lumbosacral spinal cord, Conradi & Skoglund (1969 b) showed that the axo-axonal synapses on the initial motoraxon segment disappeared during the first three weeks of postnatal life. In the present material, too, both the axon hillock and initial axonal segment were tightly covered by synapsing terminals of various sizes during the first postnatal week, but the synaptic nerve ending covering on the initial segment was scanty in the adult animals.

The identification of the axon hillock and initial segment was a greater problem in the developing Deiters nucleus than in the lumbosacral cord owing to the absence of myelination in axons sent off by neurons, in any event during the first postnatal week. Axons running from giant neurons into myelin sheaths were only seen in adult animals, and the axon hillock region could not be identified in the preceding two age groups. The few proximal axonal profiles identified in the various age groups studied during the first postnatal week resembled the proximal axonal profiles of the motoneurons in the neonatal stage described by previous investigators (Conradi & Skoglund, 1969 b), except that the initial segment lacked a granular membrane specialization. However, according to Sotelo & Palay (1968) there is no granular membrane specialization under that part of the cytomembrane that lies opposite the synaptic terminals. On the other hand, in the present material the axon hillocks and initial segments in adult animals corresponded completely to the descriptions of previous authors (Palay et al. 1968).

DEVELOPMENT OF VARIOUS KINDS OF AXON TERMINALS

The complexity of the interneuronal relationships in the lateral vestibular nucleus of the rat is brought out by the variations in ultrastructure of the nerve endings and their specialized cell junctions. A clear distinction of two types of synaptic junction as suggested by Gray (1959, 1961) could not be made in Deiters' nucleus in the rat, nor was it possible to classify the synapses into symmetric and asymmetric as suggested by Gray & Guillery (1966). The same was found with regard to the synapses in the lateral vestibular nucleus of the cat (Mugnaini et al. 1967 b).

The different types of axon terminals classified according to Sotelo and Palay (1970) were quite readily distinguished even in the early postnatal period, although they were more alike at this time than at later stages of development. Small-sized large terminals were not only larger, they were also more elongated, contained a greater amount of cell organelles and their synaptic area was shorter than large-sized small terminals.

remained clearly higher in this location than on the cell bodies of giant neurons. Similar results were obtained in quantitative studies of the ending covering in single sections and in three-dimensional reconstructions of serial sections of developing motoneurons in the spinal cord (Conradi & Skoglund 1969 a). All types of axon terminals found in the adult rat (Sotelo & Palay 1968) were represented from birth on the proximal parts of dendrites of various calibres in neurons of all sizes in the present material. No quantitative or qualitative differences in the ending covering were observed between the dendrites sent off by neurons of different sizes. In this respect the results of the present investigation differed from the results obtained in the lateral cervical nucleus of the adult cat, in which the ending covering on the dendrites of small neurons was lower than that of the larger neurons (Westman, 1971).

All kinds of axon terminals synapsed in great number on the proximal parts of the dendrites of the newborn rat, including both types of slender terminals, but were rare on the distal parts of the dendrites during the first postnatal week. These observations were in agreement with the results recently reported in other parts of the central nervous system, where the first synaptic complexes in nerve cells have been observed in the proximal parts of dendrites (Bodian 1966, Schwartz et al. 1968). Moreover in the cerebral cortex (Schwartz et al. 1968, Meller et al. 1968, Adinolfi 1971 b), in the spinal cord (Bodian, 1966, Bunge et al. 1967) and in the cerebellum (Larramendi, 1967) axo-dendritic synapses were found to develop earlier than axo-somatic synapses.

Axo-axonal synapses

Throughout the postnatal development of the lateral vestibular nucleus the same three kinds of axo-axonal synapses were observed as have previously been described in the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1970). Firstly, small axon terminals synapsed on large axon terminals, which were themselves presynaptic to the neuronal cell body or the proximal part of a dendrite. Axo-axonal synapses of this type were few in number at the newborn stage, but they clearly increased in number up to the tenth postnatal day, when they were as numerous as in adult animals. As judged by the location of the synaptic vesicle triangle, the direction of impulse transmission would be from the small to the large ones at all stages of development. In the central nervous system small axon terminals of this type, which were presynaptic to other axonal synapsing endings on the cell bodies or dendrites, have generally been considered as inhibitory (e.g. Eccles, 1961, Gray 1962).

Another type of axo-axonal synapses, already observed at the newborn stage some distance from the neuronal cell bodies and their processes, consisted of an axon terminal in contact with an adjacent axon. These axo-axonal synaptic contacts were most often seen in the first two age groups studied. During the early postnatal period they clearly decreased in number. At the end of the third postnatal week these axons began moreover to synapse on adjacent dendrites. At the end of the first postnatal month they formed fully developed axo-dendritic synaptic complexes, previously described in the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1970), in the cerebellar cortex (Gray 1961, Palay 1961) and in the lateral geniculate body (Peters & Palay 1966).

coincides, the possible existence of desmosomal junctions unrelated t the occurrence f synaptic vesicles, in addition t synaptic junctions, may be a source of error in the interpretation f pictures of immature tissue (Bunge et al 1967 Aghajanian & Bloom, 1967). The present results aff rd no clue t the question of whether membrane thickenings precede the accumul tion f sy aptic vesicles.

POSTNATAL DEVELOPMENT OF GLIAL CELLS AND THEIR RELATIONS TO NEURONS

Throughout the postn tal development of Deiters nucleus it was no major problem to distinguish between tw lines f glial cells, an astrocytic and an oligodendrocytic line The precursors of astrocytes observed t the earlier developmental stages were called "light glial cells the precursors f oligodendrocytes dark glial cells Since the purpose was t elucidat the relations between gli l cell nd neurons from the tandpoint of the development f the nucleus, it was not considered necessary to discriminate precisely between d fferent stages f maturation f the glial cells. Previously too, only the astrocytic or oligodendrocytic nature of these cells has been established in studies f the early postnatal stages of development. Hardly any ttempts ha been made t identify the arious transitional forms of the respectiv precursors in the central nervous system, which is even more difficult (Vaughn, 1969)

During the early post atal period dark glial cells with few processes were observed in small groups more distantly in the neuropil, wh le light glial cells with umerous slender extensions usually occurred si gly close to neurons From the new born stage, they were satell tes t neurons. These respecti features, sometimes even in more pronounced form, were typical f the two types f glial cell throughout the postnatal development f the nucleus until the adult stage. The total number of both astrocytes and oligodendrocytes increases during the f rst three postnatal weeks, fter wh ch slight decrease obviously occurs These conclusions were drawn from counts f precursors of v rious stages made on light micrographs mitoses were not observed either light microscopically or electronmicroscopically The results of the present study re in agreement with the observations mad in other parts of the entral nervous system (Fleischhauer 1968 V ghn, 1969) The rel tiv proportions f astrocytic nd oligodendrocytic glial cells lso rem ined quite constant d ring post natal l f except f the end f th f rst postnatal week, when the formation of new glial cells of the astrocytic line was bunda t. At the time of formation these new glial cells differed morphologically from the remainder of the astrocytes on the light microscopic lev l, although not on the fine structural level and after a few days no major differences were observed in either the light microscope or the electron microscope The production of astrocytic glial cells has been found to be most intensive during the f rst postnat l week in other parts f the central nervous system, too (e g. Smart & Leblond, 1961 Vaughn, 1969) On the basis f the present study it is not possible to say whether these glial cells are produced in the lateral vestibula nucleus or in some other nu but their greater frequency in the dorsal part f the nucleus may indicate that they migrat from the ependymal layer f the fourth brain ventricle.

It has been shown by ma y investigators (e g M t rana, 1960 Peters 1960 Bunge et l 1962 Peters, 1964 Kruger & Maxw ll, 1966 Hirano et al 1966 Bunge,

All the different axon terminals increased in size throughout the postnatal developmental period until the adult stage. The most common cell organelles — mitochondria neurofilaments, microtubules and tubules of endoplasmic reticulum — increased in number in all axon terminals throughout the postnatal period of development The increase started earlier and was more accelerated in the large terminals than in the slender and small terminals, which developed more slowly in other respects, too The number of agranular synaptic vesicles per terminal also rose throughout the period of postnatal development in all nerve endings, although most clearly in the large and slender terminals. By contrast the number of granular vesicles increased only in the small endings in the remainder of the terminals it decreased

Simultaneously with the increase in synaptic vesicles, the number of both synaptic and desmosomal junctions in the junctional zones increased in the large and slender terminals. The synaptic junctions in the slender terminals on the neuronal bodies in particular increased rapidly in number during the second postnatal week, reaching the adult level in a few days The presence of a great number of granular vesicles in the large endings on the first postnatal days and their almost complete disappearance at later stages was an interesting finding especially considering that these vesicles are probably not related to catecholamines (Fuxe 1965) Granular vesicles in the slender terminals decreased strikingly in number with advancing development. In the small axon t rminals vesicles of this kind were not observed until the fourth postnatal day but from this stage they were a constant finding and their number per small terminal increased throughout the postnatal development At the adult stage these vesicles were obviously typical of the small nerve endings.

Junctional zones, both synaptic and desmosomal junctions, were observed in the large terminals in newborn animals. Pre- and postsynaptic membrane thickenings resembling desmosomal or future synaptic junctions without synaptic vesicles were occasionally seen in the large nerve endings. There was no clearly synaptic junction between these and the cell body in the same plane of a section Without serial sectioning it is, however impossible to identify these junctions. All symmetrical membrane thickenings without adjunct synaptic vesicles were considered to be desmosomal junctions, but a proportion of them may have been developing synaptic junctions, in which the pre- and postsynaptic membrane thickenings developed before the accumulation of synaptic vesicles on the presynaptic membrane thickenings

The third type of junctional zone the gap junct on first demonstrated by Sotelo and Palay (1967 1970) between synaptic endings and mammalian nerve cells in the lateral vestibular nucleus and considered by these authors to be a con tant element of large terminals, could not be identified with certainty in the present material possibly because of the fixation used (Sotelo & Palay 1970) If junctions of this type occurred they were probably regarded as desmosomal

The formation of synapses ha been the object of numerous investigation (e g Bunge et al 1967 Tennyson 1970) Many authors have reported that local thicken ng of adjacent pre- and post synaptic plasma m mbranes are the first ign of spec alizati n and that the accumulation of synaptic esicles occurs later In th adrenal med lla (Hervonen 19 1) and the myoneural junction (Teravainen 1968) th accum lation of vesicles is reported to precede the postsynaptic thickening Since the most inten ive phase in the format on of both synaptic and desmosomal junction

SUMMARY

The postnatal development of the lateral vestibular nucleus (Deiters nucleus) of the rat was studied by both light and electron microscopy in adjacent sections in seven age groups, from the newborn to the adult stage.

The neurons were divided into three groups (giant, medium-sized and small) which differed with regard to postnatal growth and differentiation. Their nuclear size did not increase after birth in any group. The postnatal development of the giant and medium-sized neurons had many features in common. They grew most during the first fortnight and had attained adult size by the end of the first postnatal month. The rough endoplasmic reticulum and the free ribosomes and Golgi membranes became organized and increased markedly in amount before the tenth postnatal day. Neuroplasmic filaments and tubules mainly increased in amount during the second and third postnatal week. The size of the small neurons increased only slightly during the first postnatal week. They had scanty rough endoplasmic reticulum and communications between the nuclear envelope and subsurface cisterns existed even in the adult animal.

All components of the neuropil, including the dendrites and axons and glial cells and especially the processes sent off by the astrocytes, increased more in size and amount than the neuronal cell bodies. Hence, the area of the neuropil increased in size more than that occupied by the neuronal perikarya.

Most of the growth of the axons of various sizes took place during the first postnatal week before the onset of myelination. Myelination started at the end of the first postnatal week but the most intense phase of myelination was observed during the second and third postnatal weeks. Partially myelinated small axons were still found in the adult nucleus. Degenerative changes in axons and their terminals, possibly representing axonal remodelling in normal nervous tissue, were observed in the mature or nearly mature nucleus.

The dendritic tree of all neurons developed mainly during the first postnatal week, although continued growth was still clearly observed during the second week. The dendritic tree of the giant neurons increased most in size. The dendrites sent off by neurons of different sizes during the early postnatal period differed only with regard to their content of cytoplasmic organelles. These were more abundant in the dendrites coming from the larger neurons than in the dendrites sent off by the small neurons.

The neurons of various sizes differed with regard to nerve ending covering, and the differences remained the same throughout the postnatal development. The only

1968) that oligodendrocytes form the myelin sheaths of the central nervous system and that the production of these cells is highest before the onset and during the course of myelination In the present study too, the formation of new glial cell of the oligodendrocytic line was found to be most intensive during the second and third postnatal weeks, in the areas showing early myelination On the tenth postnatal day oligodendrocytes were clearly more numerous than astrocytes, and the ratio of the two types of glial cell was then about the same as in adult animals. From this age the majority of the astrocytic glial cells and an increasing proportion of the cells of the oligodendrocytic line resembled mature or almost mature astro- or oligodendrocytes with regard to fine structure and precursors of both types decreased correspondingly in number although their presence even at the adult stage indicated continued production of glial cells.

The glial cells of the astrocytic line representing various stages of maturation all formed cytoplasmic extensions into the surrounding neuropil and round the neurons and their processes, just as has been described in other parts of the central nervous system (e.g. Mugnaini & Wahlberg, 1964 Fleischhauer 1968) The oligodendrocytes also had relatively prominent cytoplasmic processes at the immature stages preceding myelination of the nucleus. This finding was in agreement with the observations previously reported in the developing optic nerve of the rat (Vaughn 1969) However the processes sent off by the astrocytic glial cells were much longer and more numerous from birth. Moreover they increased markedly in number throughout the postnatal development

The relations between neurons and neuroglial cells in Deiters nucleus attracted attention when Hydén and his co-workers started investigating the neurochemistry of the nucleus. In a series of studies they advanced the interesting theory that a symbiotic relationship exists between neurons and neuroglial cell (e.g. Hydén, 1960 Hydén & Pigon, 1960 Hamberger 1963) In these investigations it was stated that the cells in the lateral vestibular nucleus of the rabbit surrounding the neurons a satellites are mainly oligodendrocytes, and that the proportion of astrocytes in the close vicinity of neuron never exceeds 10 per cent of the neuroglia These results are not corroborated by the observations made in the present study which are in agreement with previous reports on the lateral vestibular nucleus of the adult rat (Sotelo & Palay 1968) and the adult cat (Mugnaini et al 1967 b) In the present material astrocytes were seen surrounding the neuron from birth and the oligodendrocytes were located more distantly in the neuropil throughout the period of postnatal development Oligodendrocytes were also observed in the vicinity of the smaller neurons, in particular especially in myelinated areas Thus the observation made on the postnatal developmental stages also indicated that the true satellites to neurons in the lateral vestibular nucleus of the rat are astrocytes This conclusion is consistent with recent report on other parts of the central nervous system, in which astrocytes were found to be satellites to large neurons for instance to the Purkinje cell in the cerebellar cortex (Mugnaini & Forstrønen, 1966) and, besides oligodendrocytes, to the motoneuron in the lumbosacral spinal cord (Conradi, 1969 a Conradi & Skoglund 1969 a)

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and slender on terminals w th numerous acti zones and the number of desmosomal junctions increased in larger ones

Oligodendrocytes were in the m j rity among the glial cells during almost the hole development. Astrocytes were more or equally numerous only at the end of the first postnatal week, when the production of new astrocytes was strikingly abundant From the onset f myelination the oligodendrocytes increased more rapidly in number than the astrocytes, particularly at the beginning of the second postnatal week By the tenth postnatal day mature or nearly mature glial cells of both types were ery numerous In the subsequent development of the glial cells a continued increase in astrocytic processes mainly took place.

Throughout the whole postnatal development the astrocytes were located closer to the soma f the neurons than the ol godendrocytes. They were in wide direct contact w th these by their numerous extensions. The oligodendrocytes were generally located t a greater distance from th neurons. They were invari bly separated from the neurons by astrocytic processes. From birth to the adult tage astrocytes were true satellites to neurons in the lateral estibular nucleus of the rat

exception was that two types of slender terminals appeared on the perikarya of the giant and medium sized neurons at the end of the first postnatal week.

The development of axo-somatic synapses was similar in the giant and medium-sized neurons, although these contacts were established somewhat later in the latter group. From the newborn stage the large axon terminals were the first to synapse on both giant and medium-sized neurons. These synapses did not later increase in number per cross section of either type of neuron. The axo-somatic synapses increased most in number during the first postnatal week. This increase was mainly due to a multiplication of the synapses formed by small terminals, in particular in the giant cells. The same trend was observed in the giant and medium-sized neurons at the beginning of the second postnatal week simultaneously with an increase of both types of synapsing slender terminals. The axo-somatic synaptic connections of both types of neuron were most numerous on the tenth postnatal day. Later their number remained the same or decreased slightly. Only small axon terminals synapsed on small neurons. These synapses increased in number only during the first postnatal days and remained low during the later postnatal development.

All types of axo-dendritic synapses on the proximal parts of the dendrites were numerous from birth. The moderate increase in the number of axo-dendritic synapses on the proximal parts of dendrites observed during th first postnatal week was mainly due to an increase in the synapses made by small terminals. During the first and second postnatal weeks the number of synapsing small terminals increased more on the distal parts of the dendrites than on their proximal parts. New synaptic connections with the terminal segment of the dendrites seemed to develop even at the adult stage in dendritic expansions.

Axo-axonal synapses consisting of small axon terminals synapsing on large axon terminals, which were presynaptic either to the neuronal soma or the proximal part of a dendrite, increased in number up to the tenth postnatal day.

Axo-axonal synapses between axon terminals and axons of various sizes were seen in relative abundance in the neuropil during the early neonatal period. They rapidly decreased in number being rare at the tenth postnatal day and thereafter. Towards the end of the first postnatal month these synapsing axon terminals also began to synapse on adjacent dendrites, forming axo-dendritic synaptic complexes.

During the first postnatal week the number of axo-axonal synaptic terminals was high on both the axon hillock and the initial axonal segment, but in the latt r it their number reduced during later postnatal development.

From the newborn stage the axon terminals of various kinds to a considerable degree resembled the corresponding structures in the mature nucleus with regard to shape size contents and junctional zones. The terminals of all different types increased in size throughout the period of postnatal development but the large axon terminals and the two types of slender terminals increased considerably more in iz than the small terminals. The common cytoplasmic organelles, such as mitochondria neurofilaments and microtubules, increased in amount in all nerv endings throughout the postnatal development. The amount of granular synaptic esicles increased in the large and the two types of slender terminals, but not in the small terminals, which in turn had increasing amounts of granular vesicles. The number of synaptic junct ons per terminal rose relatively evenly throughout the postnatal development in l rge

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I W S MAIR

From the Department of Surgery (Otolaryngology) University
of Chicago, Chicago, Illinois and the Department of Otolaryngology
University of Tromsø Norway

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Anomalies of pigmentation are often found in association with hereditary deafness in several animal species and man. Waardenburg (1951), in the first definitive description of the syndrome which now bears his name, described the occurrence in man of congenital deafness and pigmentary defects of the iris and head hair This syndrome was found to constitute a well demarcated genetic complex with an autosomal dominant inheritance (Cotterman, 1951) Several authors (Fisch, 1959 DiGeorge et al 1960) have reported regions of cutaneous depigmentation as a fairly frequent feature of the Waardenburg syndrome Ziprkowski et al (1962) reported a family in which deafness and pigmentation anomalies were inherited through a sex linked recessive gene. Other differently inherited syndromes in which deafness is associated with varying degrees of hypopigmentation have been described by Tietz (1963) and Woolf et al. (1965).

Among animals, the most widely recognised species affected by these traits is the white cat, but several species of dog present hearing loss and pigmentation abnormalities due to the influence of the merle gene This has been described in bull and fox terriers (Wright, 1918), collie dogs (Mitchell, 1935) and the Norwegian dunker hound (Sorsby & Davey 1954). The dalmatian is not a merle dog, though also affected by hereditary deafness. Other animal species in which similar syndromes are found are the white mink (Sugiura & Hilding, 1970) the rabbit (Nachtsheim, 1941) and several genotypes of mice (Deol, 1970).

This study was supported in part by Grant NB-0682 from the National Institute of Health, Washington.

It is important in this context to differentiate between albinism and the white spotting or hypopigmentation which is the abnormality found in all the above mentioned species. In the former condition melanocytes can be identified in the skin as clear cells, or amelanotic melanocytes, but do not possess the ability to produce pigment (Billingham & Silvers, 1960). In the white areas of hypopigmented animals, however melanocytes cannot be demonstrated although pigment is found in the retina (Markert & Silvers, 1956) showing that the capacity to produce pigment is retained by the animal. Albinos are completely devoid of pigment, but generally have normal hearing, although Margolis (1962) and Ziprkowski & Adam (1964) have described recessive albinism and deafness in man.

The difficulties encountered in differentiating between hereditary and acquired forms of deafness in man have been frequently stressed in the recent literature (Altmann, 1964 Lindsay & Matz, 1966) and it has been conclusively demonstrated that the Scheibe or cochleo-saccular type of inner ear degeneration can occur in both aetiological groups (Schuknecht, Igarashi & Gacek, 1965). It was hoped that a detailed investigation of the hereditary form of deafness in the white cat might give additional information helpful in the solving of problems of aetiology in human deafness. For maximum clarity and conciseness in the presentation of the results it was decided to group the material in separate publications viz., heredity development of the vestibular degeneration maturation of the cochlea in normal hearing animals, development of the cochlear degeneration degeneration of the

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first order cochlear neuron and finally the findings in the primary cochlear nuclei The details of the relevant material and methods will be presented in each subsequent publication

MATERIAL AND METHODS

A white cat stock of 110 animals was gradually accumulated over a number of years. This population consisted partly of white coat adult animals received fortuitously in the animal quarters, and of an approximately equal number of animals, both white and colour coat, bred from white cats already in our possession

The investigation commenced in 1964 with the acquisition of a pair of white cats The male member of this pair Romeo was used for breeding purposes, first with the other original animal Juliet and subsequently with a number of other animals including his own offspring. In addition four adult white cats of known heredity were obtained from the National Institute of Health Washington. These two sources accounted for approximately half of the white cat stock the remainder being of unknown heredity and acquired from a variety of sources. The original stock of 110 animals was reduced to 96 due to premature death or escape from the animal quarters Temporal bone histology was available for all these 96 animals.

The coat colour was recorded in all animals and the coat length in the majority Animals with the least admixture of colour in the coat were classified as non-white or coloured Hair length was readily classifiable as either long or short Coat colour and hair length could be assessed from birth. Iris colour was also evaluated and recorded as blue i e completely blue iris without admixture of other colours, or as yellow in which group yellow green brown and all forms of heterochromia were included As all kittens have blue eyes in the early post partum stage before the eyes open spontaneously it was not found possible to make a reliable estimate of eye colour earlier than fourteen days of age

The cochlear potentials were recorded from round window electrodes in all animals and vestibular testing performed in approximately one third. Heidenhain s Susa fixative was used for intravital perfusion throughout the series and the temporal bones and hind brains were removed usually in separate blocks and processed for histological examination with the light microscope Animals were sacrificed at ages varying from a few hours after birth up to approximately eight years of age. It was found that the presence or absence of hearing could not be established with certainty prior to the seventh day post partum. The earliest reliable light microscopical evidence of end organ degeneration was also found after seven days of age. Therefore, in this series, the presence or absence of hearing and of histological inner ear degeneration have been established only for animals more than one week old

RESULTS

The age distribution of the 96 animals in the white cat stock is shown in Table 1 The association between coat colour and inner ear degeneration in the 76 animals over the age of one week is shown in Table 2. All of the coloured coat animals had bilaterally normal hearing and temporal bone histology apart from the occasional presence of middle-ear infection Inner ear degeneration and absence of the round window potentials were found in 34 of the 66 white coat animals (51 5 %) being unilateral in eight (12.2 %) The data on coat length are unfortunately incomplete there being no record in 15 of the 66 white coat animals. Table 3 shows the association between coat length and inner

Table 1 *Age distribution of white cat stock in days (n = 96)*

Age in days	Coat colour White	Coloured	Total
0–7	17	3	20
7 14	8	1	9
15 +	58	9	67
Total	83	13	96

Table 2. *Association between inner ear degeneration and coat colour in cat population older than 7 days (n = 76)*

Inner ear degeneration	Coat colour		
	White	Coloured	Total
Bilateral	26	0	26
Unilateral	8	0	8
Absent	32	10	42
Total	66	10	76

Table 3. *Association between inner ear degeneration and coat length in white cat population older than 7 days (n = 66)*

Inner ear degeneration	White coat length			
	Long	Short	Unknown	Total
Bilateral	16	5	5	26
Unilateral	3	4	1	8
Absent	5	18	9	32
Total	24	27	15	66

ear degeneration. 79 % of the long coat animals had degeneration in one or both ears as against only 33 % of the short hairs. However animals with short hair accounted for 50 % of the unilateral degeneration group, whereas short hair was present in only 19 % of those with bilateral inner ear degeneration.

Eye colour was recorded for all of the 58 white coat animals over the age of 14 days (Table 4). Inner ear degeneration was present in

Table 4. *Association between inner ear degeneration and eye colour in white cat population older than 14 days (n = 58)*

Inner ear degeneration	Eye colour			
	Blue blue	Blue-yellow	Yellow yellow	Total
Bilateral	13	5		20
Unilateral	4	3	1	8
Absent	3	12	15	30
Total	20	20	18	58

Table 5. *Association between inner ear degeneration and ipsilateral eye colour (n = 116)*

Inner ear degeneration	Ipsilateral eye colour		
	Blue	Yellow	Total
Present	38	10	48
Absent	23	45	68
Total	61	55	116

Table 6. *Eye colour in white cats with unilateral inner ear degeneration (n = 8)*

Eye colour		
Ipsilateral	Contralateral	Total
Blue	Blue	4
Blue	Yellow	3
Yellow	Yellow	1
Yellow	Blue	0

85 % of blue-blue animals, in 40 % of blue yellows and in only 16.7 % of yellow yellows. Of the 58 animals in this group 20 had bilateral and 8 unilateral inner ear degeneration. Degeneration was therefore present in 48 of 116 ears. The association between inner ear degeneration and ipsilateral eye colour is shown in Table 5. Blue eye colour is again shown to be more frequently associated with inner ear degeneration than is yellow (38:10). The eight unilaterally deaf animals are presented in Table 6. This shows a

Table 7. *Inner ear degeneration, eye colour and white coat length in cat population older than 14 days (n = 58)*

Eye and coat characteristics	Inner ear degeneration			
	Bi-lateral	Uni-lateral	Absent	Total
Blue–blue–long	8	3	1	12
Blue–blue–short	3	1	0	4
Blue–yellow–long	2	0	2	4
Blue–yellow–short	1	2	8	11
Yellow–yellow–long	0	0	2	2
Yellow–yellow–short	1	1	9	11
Coat length unknown	5	1	8	14
Total	20	8	30	58

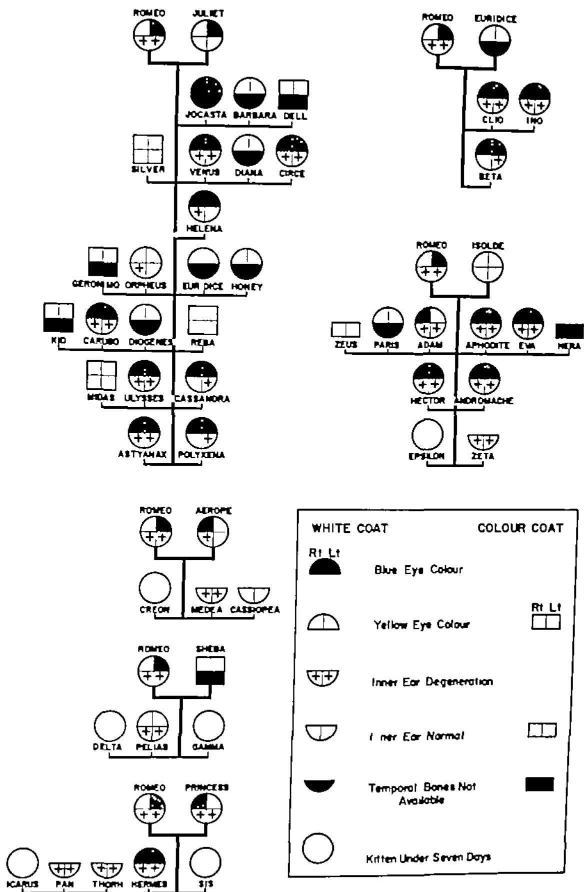


Fig 1 Pedigrees of Romeo's descendents Males are shown to the left of the thick vertical lines and females to the right Symbols are explained in the accompanying legend.

Table 8. *Incidence of inner ear degeneration in the different genetic groups of white coat cats older than 7 days (n = 66)*

	Heredity			
	Romeo	NIH*	Unknown	Total
Total animals	25	4	37	66
Bilateral degeneration	19	1	6	26
Unilateral degeneration	5	0	3	8
Total ears with degeneration	43	2	15	60
Total normal ears	7	6	59	72
Incidence degeneration,	86	25	20.3	45.4

NIH National Institutes of Health, Washington

negative correlation for blue eye colour on the contralateral side i.e. if the ipsilateral eye colour is yellow then the contralateral is not blue. The data for eye colour and coat length are combined in Table 7. Inner ear degeneration was present in all four of the blue-blue-shorts and in 11 of the 12 blue-blue-longs. Both of the yellow-yellow-longs had hearing bilaterally.

In Fig. 1 are presented the results of mating one of the animals, Romeo, with various females, including one of his own offspring, Euridice. Unfortunately several of the temporal bones from this group were not available for histological examination due to premature death. None of the colour coat animals had blue eyes or inner ear degeneration. The mating of Romeo and Princess, both bilaterally deaf animals, produced five offspring, three with bilateral inner ear degeneration, but the remaining two were unfortunately sacrificed at an age when hearing could not be reliably assessed. The material is therefore inadequate for a proper investigation of the penetrance of the gene for deafness.

The distribution of inner ear degeneration in the different heredity groups is shown in Table 8. There were 66 white coat animals of more than seven days of age which gives a total of 132 ears. Inner ear degeneration was present in 60 of those ears, 26 animals having bilateral and 8 unilateral degeneration. The incidence of inner ear degeneration in the population as a whole is therefore 45.4 %. When only Romeo's descendents are analysed the incidence of inner ear degeneration is 86 %, whereas the figure for the presumably heterogeneous group of animals of unknown heredity is 20.3 %.

DISCUSSION

The association between white coat colour, blue iris colour and deafness in cats was regarded as invariable by the earliest observers (Bree, 1829; Sichel, 1847; Darwin, 1859). However, Tait (1883) reported that deafness could occur either with blue or yellow eye colour, but believed that only white coat males were affected. Stevens (1884) disagreed with the latter finding and reported the occurrence of deafness in blue-eyed, white coat females. Przibram (1907) concluded that the hearing loss was always on the side of the blue eye in animals with different eye colours, a finding which is corroborated by our series of unilaterally deaf animals. Beaumont (1911) found the association between blue eye colour and deafness to be constant, and believed that animals with only one eye blue were never deaf. The same author also reported blue-eyed offspring amongst the descendents of animals with bilateral yellow eye colour. Breeding experiments carried out by Whiting (1918) established that white coat colour was inherited as a Mendelian dominant, but that the inheritance of iris colour was very irregular. Wright (1918) and Bamber (1927) found a tendency for asymmetrically coloured eyes to run in families, but the asymmetry was unspecific and the mode of inheritance unknown.

The earlier literature therefore contains many contradictory statements, but unfortunately many of the later contributions have not helped appreciably to clarify the situation. The literature of recent years contains a few reports on deafness in the white cat, with descriptions of only the physiological and histological findings for short series of three or four animals (Wolff

1942 Wilson & Kane, 1959 Suga & Hattler 1970) Only two publications contain studies of larger series, both, however being confined to younger animals (Bosher & Hallpike, 1965 Bergsma & Brown, 1971)

Bosher & Hallpike (1965) reported a series of 28 white cats, but eye colour and coat length were not mentioned and the oldest animal was sacrificed at 281 days. Of the seven animals used for breeding purposes, six were bilaterally deaf and the seventh had unilateral ear degeneration. The penetrance of the inner ear degeneration in that series was about 80% More recently Bergsma & Brown (1971) in a comprehensive genetic study of young animals found that blue eye colour tended to be bilateral and that heterochromia in parents did not predispose to heterochromia in the offspring. Further the autosomal dominant gene had complete penetrance for white coat colour but the ear defect was only about 43 % penetrant.

The present series supports the latter conclusions. The incidence of inner ear degeneration in the entire white cat population was 45 4 %, whilst in the group of Romeo s descendents the penetrance of 86 % is of the same order of magnitude as the 80 % reported by Bosher & Hallpike (1965). In our heterogeneous white cat population the incidence of inner ear degeneration was 20.3% which is close to the penetrance of 27 % reported by Bergsma & Brown (1971) for the heterozygote and is identical to the penetrance of 20 reported for the inner ear degeneration in Waardenburg s syndrome (Fisch, 1959)

CONCLUSIONS

This material does not permit a detailed statistical analysis, but the following conclusions may be drawn

1 Hereditary deafness in cats occur only in animals with white coats

2 Deafness may be unilateral or bilateral and is found in both sexes.

3 The inner ear degeneration is more often associated with blue eye colour but the association is far from constant

4 Animals with different eye colours may have either bilateral or unilateral degeneration, but in the latter case the degeneration is on the side of the blue eyes.

5 Long coat hair is more often associated with inner ear degeneration (79) than is short hair (33) The latter however is more frequently associated with unilateral hearing loss.

6 The incidence of inner ear degeneration in a random white cat population is 20.3 % but increases to 86 when hereditary hearing loss is present in one or both of the parents.

ZUSAMMENFASSUNG

Die Beziehungen zwischen Farbe des Pelzes, Haarlänge, Irisfarbe und erblicher Taubheit werden für eine Gruppe von 96 Katzen mitgeteilt. Das Auftreten von Innenohr Degeneration wechselt von 20 bis 86 es hängt von der genetischen Struktur der Population unter bestimmten Bedingungen ab. Es wird auf zukünftige Arbeiten über erbliche Taubheit bei der weissen Katze hingewiesen

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1942 Wilson & Kane, 1959 Suga & Hattler 1970) Only two publications contain studies of larger series, both, however being confined to younger animals (Bosher & Hallpike 1965 Bergsma & Brown 1971)

Bosher & Hallpike (1965) reported a series of 28 white cats but eye colour and coat length were not mentioned and the oldest animal was sacrificed at 281 days. Of the seven animals used for breeding purposes, six were bilaterally deaf *and the seventh had unilateral ear degeneration.* The penetrance of the inner ear degeneration in that series was about 80 %. More recently Bergsma & Brown (1971) in a comprehensive genetic study of young animals found that blue eye colour tended to be bilateral and that heterochromia in parents did not predispose to heterochromia in the offspring Further the autosomal dominant gene had complete penetrance for white coat colour but the ear defect was only about 43 % penetrant

The present series supports the latter conclusions The incidence of inner ear degeneration in the entire white cat population was 45 4 %, whilst in the group of Romeo s descendents the penetrance of 86 % is of the same order of magnitude as the 80 % reported by Bosher & Hallpike (1965) In our heterogeneous white cat population the incidence of inner ear degeneration *was* 20 3% which is close to the penetrance of 27 % reported by Bergsma & Brown (1971) for the heterozygote and is identical to the penetrance of 20 % reported for the inner ear degeneration in Waardenburg s syndrome (Fisch, 1959)

CONCLUSIONS

This material does not permit a detailed statistical analysis, but the following conclusions may be drawn

1 Hereditary deafness in cats occurs only in animals with white coats

2. Deafness may be unilateral or bilateral and is found in both sexes

3 The inner ear degeneration is more often associated with blue eye colour but the association is far from constant

4 Animals with *different* eye *colours* may have either bilateral or unilateral degeneration, but in the latter case the degeneration is on the side of the blue eyes.

5 Long coat hair is more often associated with *inner ear degeneration* (79) *than is* short hair (33 %) The latter however is more frequently associated with unilateral hearing loss.

6 The incidence of inner ear degeneration in a random white cat population is 20.3 %, but increases to 86 % when hereditary hearing loss is present in one or both of the parents.

ZUSAMMENFASSUNG

Die Beziehungen zwischen Farbe des Pelzes, Haarlänge, Irisfarbe und erblicher Taubheit werden fur eine Gruppe von 96 Katzen mitgeteilt. Das Auftreten von Innenohr Degeneration wechselt von 20 % bis 86 es hängt von der genetischen Struktur der Population unter bestimmten Bedingungen ab Es wird auf zukunftige Arbeiten über erbliche Taubheit bei der weissen Katze hingewiesen.

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MATERIAL AND METHODS

A white cat stock of 96 animals was acquired over a number of years. Sixty-six of these animals had completely white coats and could be assessed for the presence or absence of hearing. Details of this population have been presented in part I of this volume (Mair I).

Vestibular testing was performed in thirty animals. Button electrodes were inserted at the glabella and in the malar bones for the electronystagmographic recording of horizontal eye movements. Posture, locomotion and righting reflexes were observed and positional, optokinetic, oscillatory and caloric tests performed. The investigational techniques have been described elsewhere (Mair & Fernández, 1966). The youngest animal in whom vestibular testing was performed was aged six months and the oldest was eight years of age.

Cochlear potentials were recorded from a round window electrode in all 96 animals. Bilateral hearing loss was found in 26 and unilateral in 8 of the white coat animals. The animals were then perfused by the standard intravital method of fixation using Heidenhain's Susa reagent, survival periods varying from the first postnatal day up to eight years of age. In the vast majority of cases the temporal bones and hind brains were removed in separate blocks and processed for light microscopy. The temporal bones were imbedded in celloidin and orientated with the midmodiolar axis of the cochlea in the horizontal plane. Serial sections were cut at a thickness of 20 microns and every tenth section stained with haematoxylin and eosin. The vestibular labyrinth was studied systematically and the findings in the deaf ears compared with age matched white coat hearing animals. For purposes of comparison, the temporal bones from 13 kittens and 10 adult cats from colour coat stock were examined for the distribution of pigment. The extent of pigmentation was recorded in each animal from the contra-macular wall of the utricle and from the slopes of the crista in each canal (Deol, 1970).

Table 9 *Age distribution and incidence of inner ear degeneration in the thirty white coat cats subjected to vestibular testing*

Inner ear degeneration	Age in months			Total
	6–12	12–24	24+	
Bilateral	3	4	7	14
Unilateral	1	2	1	4
Absent	0	0	12	12
Total	4	6	20	30

RESULTS

1 *Functional examination*

The complete battery of vestibular tests was performed in 30 animals. Subsequent measurement of cochlear potentials showed that 12 of the 30 had normal hearing bilaterally, 14 were bilaterally deaf and in 4 the hearing loss was confined to one ear. The incidence of inner ear degeneration and the age distribution of the 30 white coat animals tested are shown in Table 9.

No disorders of posture or locomotion were observed and the righting reflexes were normal for all 30 animals. The remaining 66 animals not subjected to the full vestibular testing procedure were, however, observed clinically and no disorders of equilibration could be ascertained in the course of the animals' normal range of activity. Positional nystagmus was neither observed nor recorded in any of the 30 animals tested. The optokinetic and rotatory responses were symmetrical and non-pathological. No abnormalities were detected on bithermal caloric irrigation (Fig. 2). Oscillation responses were also normal (Fig. 3).

2 *Histological examination*

The osseous labyrinth presented no abnormalities. The membranous labyrinth from all hearing ears, both from white coat and colour coat animals, was unremarkable. The membranous semicircular canals and the utricle of all deaf ears were of normal dimensions and the light-microscopical appearances of the neuroepithelium of the cristae and the utricular maculae were indis-

II Vestibular Function and Histopathology

Abstract An electronystagmographic study of vestibular function in the deaf white cat revealed no functional abnormalities. Histological changes were confined to the saccule and increased as a function of age. Collapse of the saccular wall was followed by encapsulation of the otolithic membrane. At all stages in the degenerative process the region of the saccule nearest the cochlea was more severely affected than the more posterior areas. The degenerative process extends radially from the ductus reuniens and shows no correlation with the degree of inner ear pigmentation.

The pars inferior of the membranous labyrinth appears to be more susceptible to a variety of nocuous agents than are the phylogenetically older utricle and semicircular canals The cochleo-saccular or Scheibe, type of inner ear degeneration has been described in hereditary human deafness (Scheibe, 1891 Ward et al 1962), in deafness due to maternal rubella (Lindsay et al., 1953) and in presumed viral labyrinthitis (Lindsay & Hemenway 1954 Lindsay Davey & Ward 1960) Cochleo-saccular degeneration has also been demonstrated in aged humans and animals (Schuknecht, Igarashi & Gacek, 1965) A similar type of degeneration has been found in several species of animals afflicted by hereditary deafness Among those species reported in the literature are the white mink (Sugiura & Hilding, 1970) several species of dog (Igarashi et al 1972) various mouse mutants (Deol, 1968) and the white cat (Bosher & Hallpike 1965)

The first description of the temporal bone findings in deaf white cats was that of Rawitz in 1897 but the condition of the vestibular organs was not mentioned Alexander (1900) reported similar cochlear findings, but noted in addition that the saccular wall was collapsed and that there was degeneration of the saccular macula The finding of cochleo-saccular degeneration in the deaf white cat has since been confirmed by several authors (Howe, 1935 Bosher & Hallpike, 1965 Suga & Hattler 1970), but several publications contain either contradictory statements or the results of inadequate investigations. Wolff (1942) stated that the 'vestibular end-organs and ganglion cells appeared to be in good condition in a deaf adult white cat. In three of the four temporal bones examined by Wilson & Kane (1959) no mention of the vestibular end-organs is made. The fourth is described as showing no obvious vestibular disturbances" A more recent publication on this subject (Suga & Hattler 1970) contains descriptions of the histological findings in three animals. All had normal utricles and semicircular canals, but obliteration of the saccular lumen with degeneration of the macula was found in two The saccule in the third animal a deaf adult, was reported as showing no abnormalities.

Hereditary inner ear degeneration has been most systematically studied in the mouse, in which species approximately thirty mutants with inner ear abnormalities have been investigated (Deol 1968) Most of these mutants have behavioural disorders known as the waltzing syndrome but considerable differences exist between the genotypes. The time course of the vestibular end-organ degeneration has been extensively studied in many of these mutants (Deol 1968)

The literature on vestibular findings in the deaf white cat contains no studies comparable to those in the mouse There are no reports on vestibular physiology and the development of the degeneration in the vestibular labyrinth has not been studied in any detail This paper contains the results of vestibular testing of a white cat stock and a detailed description of the light microscopical findings in the vestibular labyrinth from a series of deaf animals.

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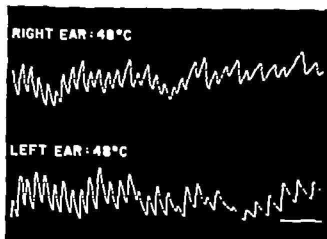


Fig Hot caloric responses from an adult white cat with bilateral cochleo-saccular degeneration showing period of maximal response. An upward deflection in *this and the succeeding figure indicates horizontal eye* movement towards the left and a downward deflection indicates similar movement to the right. Time marker = 1 second.

tinguishable from those of hearing ears. The canalicular and utricular nerves were unremarkable. Pathological findings in the vestibular labyrinth were confined to the saccule and occurred only in those ears shown to be deaf by cochlear electrophysiological studies. No histological abnormalities were found in animals of seven days of age or younger The development of the saccular degeneration was found to be a function of increasing age

The youngest animal with unequivocal hearing loss was aged eight days, and the only histological sign of vestibular abnormality at this stage is a change in the configuration of the lateral wall of the saccule The anterior portion of the lateral saccular wall has a wavy outline and appears to be in the process of descending towards the macula (Fig 4 A) At this stage the cochlear duct is of almost normal dimensions, but in the upper basal coil Reissner's membrane has a similar wavy outline although this is less pronounced than in the saccule (Fig. 4 A) Later stages of this process in adult animal are shown in Fig 4 B and Fig 5 D The saccular wall is seen to be in contact with the full extent of the macula producing almost complete obliteration of the lumen This latter is, however never complete as the posterior part of the saccular lumen always remains patent

Once the process of saccular degeneration has commenced it proceeds very rapidly At day eight the sensory and supporting cells of the saccular macula reveal no abnormalities and the sole pathological finding is the previously described change in the antero-lateral wall At day ten the saccular wall has collapsed still further and is in contact with the anterior pole of the macula and of the otoconia layer (Fig 5 B) The latter appears to have increased in thickness. The sensory cells at this stage appear mature and healthy and indistinguishable from a hearing animal of similar age but the hairs are deflected posteriorly and have assumed a position almost parallel to the free surface of the neuroepithelium. Two days later at day twelve the saccular wall is in contact with the entire extent of the otolithic membrane (Fig. 5 C) The individual otoconia are larger and have a more intensely basophilic stain. Between the free surface of the neuroepithelium and the deep surface of the otoconia layer and apparently applied to the latter a thin layer of flattened cells is found The otoconia layer thus appears to be surrounded by a membraneous covering. The sensory cells still have a healthy appearance but there is a definite reduction in the number of hairs. A few free nuclei

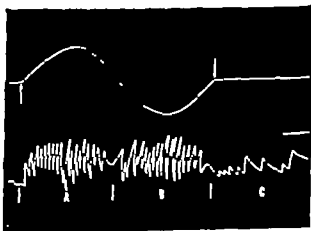


Fig 3 Oscillation responses from an adult white cat with bilateral cochleo-saccular degeneration The upper tracing shows the movement pattern of the rotating platform and the lower the provoked horizontal eye movements. Time marker = 1 second

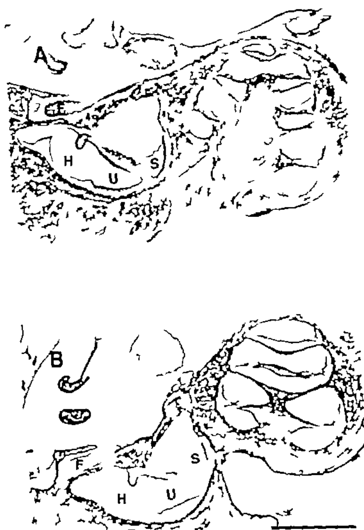


Fig. 4. Low power view of saccule (*S*) utricle (*U*) and horizontal canal (*H*), with approximately mid-modiolar section of the cochlea. Marker 1 mm. *F* = facial nerve. (A) Deaf, white kitten aged 8 days. Note the wavy outline of the antero-lateral saccular wall and of Reissner' membrane in the upper basal coil. (B) Adult, deaf white cat showing almost complete obliteration of the saccular lumen and the cochlear duct in all coils.

are present in the space between the neuroepithelium and the membrane-enclosed otoconia.

The animals sacrificed at day twenty and day twenty-six both proved to have unilateral hearing loss, thus permitting direct comparison of the saccular findings in hearing and deaf ears at this important stage in the development of the degenerative process.

A high-power view of the saccule from the healthy ear of the twenty day animal is shown in Fig. 6 A, and a similar area from the opposite and deaf ear is presented in Fig. 6 B. In the week which has elapsed from day twelve to day twenty the following changes have occurred in the saccule. The otoconia layer is definitely thicker on the pathological side and the individual otoconia are larger and more basophilic staining. The saccular wall remains collapsed, but the membranous layer on the deep surface of the otoconia is more prominent and varies from one to two cells in thickness. Very few hairs can be identified on the free surface of the neuroepithelium and there is an appearance of vacuolisation in the supranuclear area of the sensory cells. The free nuclei

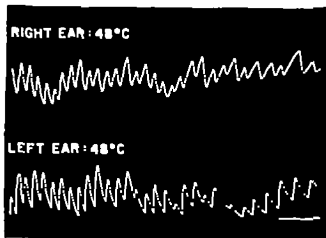


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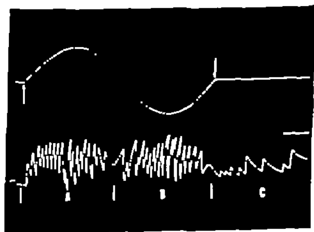


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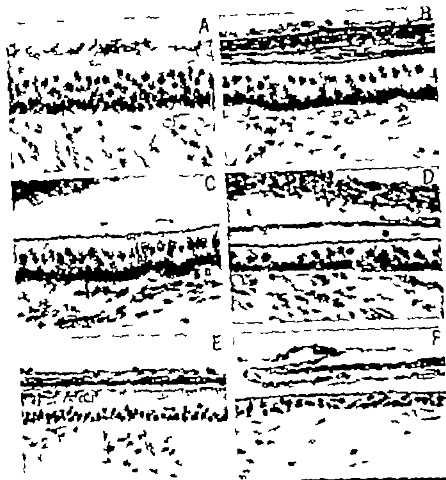


Fig. 6. Higher power view of saccular macula and otoconia layer from approximately the central portion of the macula in five white coat animals. Marker 50 microns. (A) Right saccule from unilaterally deaf animal aged 20 days showing normal appearance from the hearing ear. (B) Pathological left saccule from same animal shown in 5 A, from the opposite, deaf ear. Both surfaces of the otoconia layer are enclosed in cellular membranes. (C) Pathological left saccule of cat aged 26 days. The crenellated layer of globular vesicles projecting above the surface of the neuroepithelium can be identified. (D) Pathological right saccule from cat aged 43 days. The globular vesicles shown in 5 C are replaced by a layer of homogeneous, eosinophilic precipitate. The neuroepithelium is markedly reduced in height and there is reduction in numbers of sensory cells. (E) Pathological right saccule of animal aged 14 months. The layer of precipitate shows fragmentation and there is a much greater degree of sensory cell loss. (F) Pathological left saccule of adult cat aged 8 years. Sensory cells are absent and the supporting cells are degenerating with loss of cell outlines and pyknotic nuclei.

ly eosinophilic staining, amorphous precipitate which covers the entire surface of the macula. There is considerable sensory cell loss, most marked at the anterior pole and the height of the neuroepithelium is definitely reduced. Most of the remaining sensory cells have acuolated cytoplasm and there are many free pyknotic nuclei and degenerating cells present in the space between the macula and the otoconia layer.

From two to fourteen months the degenerative process consists of an increasing sensory cell loss and an increase in the membranous layers surrounding the otoconia. Specimens were available at six and ten months. The saccule from a fourteen month deaf ear is shown in Fig. 6 E. Three layers of flattened cells are present on the deep surface of the otoconia. Very few sensory cells remain, and these are found only at the posterior

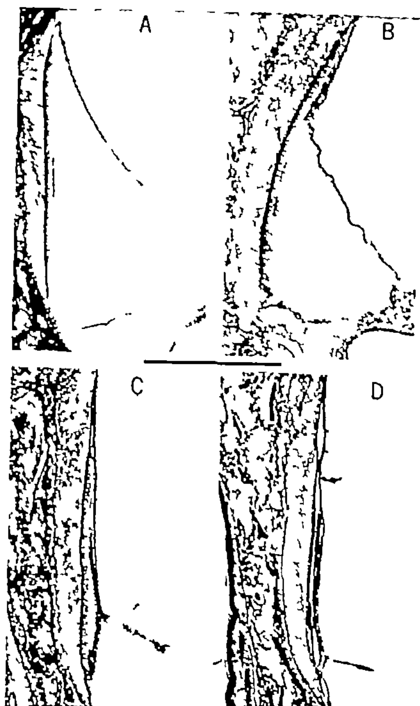


Fig 5 Low power view of the left saccule orientated with the anterior or juxta-cochlear pole superiorly Marker = 500 microns (A) Colour coat kitten aged 10 days with normal appearance of the saccule. (B) White coat kitten aged 10 days with bilateral deafness showing commencing obliteration of the saccular lumen. (C) White coat kitten aged 1 days with bilateral deafness showing almost complete obliteration of the saccular lumen. (D) Adult, white cat with bilateral deafness showing obliteration of the saccular lumen and advanced macular degeneration

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Approximately one week later at day twenty six, the most striking development is the appearance of globular vesicles projecting from the free surface of the sensory cells (Fig 6 C). These give the appearance of a crenellated layer above the neuroepithelium No hairs can be identified and there is a minimal but definite reduction in the numbers of sensory cells at the anterior or juxta-cochlear pole of the macula.

In this series, the next animals with inner ear degeneration were four bilaterally deaf cats in the age group forty three to fifty seven days The saccule of one of these animals is shown in Fig 6 D and is typical of this stage of degeneration. The otoconia layer is surrounded by the membranous covering which, on the deep surface is one cell thick posteriorly and two or three cells thick anteriorly The globular vesicles present at day twenty-six have apparently coalesced, and are replaced by an homogeneous layer of slight

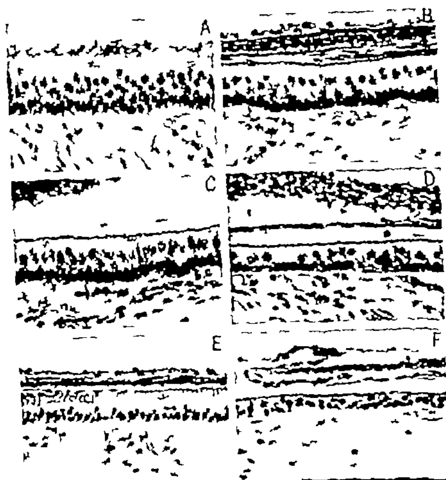


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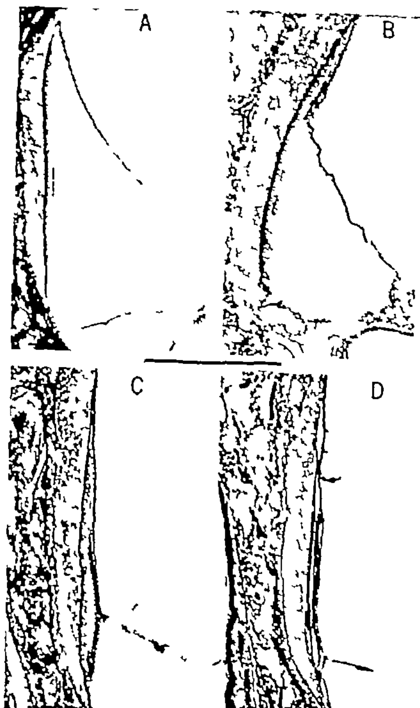


Fig 5 Low power view of the left saccule orientated with the anterior or juxta-cochlear pole superiorly Marker = 500 microns. (A) Colour coat kitten aged 10 days with normal appearance of the saccule. (B) White coat kitten aged 10 days with bilateral deafness showing commencing obliteration of the saccular lumen. (C) White coat kitten aged 1 days with bilateral deafness showing almost complete obliteration of the saccular lumen (D) Adult, white cat with bilateral deafness showing obliteration of the saccular lumen and advanced macular degeneration

in the space between the neuroepithelium and the otoconia are more numerous and pyknotic.

Approximately one week later at day twenty six, the most striking development is the appearance of globular vesicles projecting from the free surface of the sensory cells (Fig 6 C) These give the appearance of a crenellated layer above the neuroepithelium. No hairs can be identified and there is a minimal but definite reduction in the numbers of sensory cells at the anterior or juxta-cochlear pole of the macula.

In this series, the next animals with inner ear degeneration were four bilaterally deaf cats in the age group forty three to fifty-seven days. The saccule of one of these animals is shown in Fig. 6 D and is typical of this stage of degeneration. The otoconia layer is surrounded by the membranous covering which on the deep surface is one cell thick posteriorly and two or three cells thick anteriorly The globular vesicles present at day twenty-six have apparently coalesced, and are replaced by an homogeneous layer of slight



Fig. 8. Area of saccular macula from the left ear of a 10 month bilaterally deaf white cat showing ganglion cell in the neuroepithelium (arrow).

pose, i.e. deaf ears in white coat animals, hearing ears in white coat cats and hearing ears in animals with coloured coats. In each group pigment accumulation varied from considerable to complete absence. There was, however, a tendency for pigment to increase in quantity with increasing age in all three groups. The distribution of pigment was symmetrical in the ears of all unilaterally deaf animals irrespective of age.

Two animals, aged respectively ten and fourteen months, presented a rather unexpected finding in the degenerating saccular macula. Two cells were found in the former and one in the latter which had the typical light microscopical appearance of ganglion cells from Scarpa's ganglion (Fig. 8). There was no evidence of ganglion cell loss in Scarpa's ganglion of deaf adult animals.

DISCUSSION

Vestibular studies in human hereditary deafness have generally shown normal function (Arnvig, 1955), but depressed responses have been reported in Usher's (Vernon, 1969) and in Pendred's syndromes (Fraser et al., 1960). In the family with partial albinism and deaf mutism reported by Ziprkowski et al. (196.) caloric testing revealed absent responses. Anomalies of pigmentation are also present in Waardenburg's syndrome and Marcus (1968) has shown that disturbances of vestibular function occur more commonly than does hearing loss. However tomography in two of his cases revealed cochlear and canal hypoplasia and absence of the posterior canal, whereas the sole report of the histological findings in this syndrome describes degeneration confined to the membranous pars inferior of the inner ear (Fisch, 1959).

Anomalies of locomotion accompany the hereditary inner ear degeneration in several mouse mutants (Deol, 1968), but locomotor abnormalities have never been described in man, cats or dogs (Altmann, 1964). The vestibular studies from the present series of deaf white cats have not revealed evidence of malfunction. Even adult animals with complete loss of saccular sensory cells have no demonstrable disturbance of voluntary or provoked eye movements, under the experimental conditions of this investigation, and this applies equally to unilateral and bilateral lesions.

Detailed studies of the time course of vestibular end-organ degeneration in hereditary deafness have been made only in the mouse. Degeneration of the saccular macula occurs considerably later than in the cochlea of these mutants (Deol, 1968). In the present white cat material, reduction of the saccular lumen and volume changes in the scala media of the cochlea occur simultaneously. The process of saccular degeneration commences at the anterior pole and a time lag was consistently found which became pro-

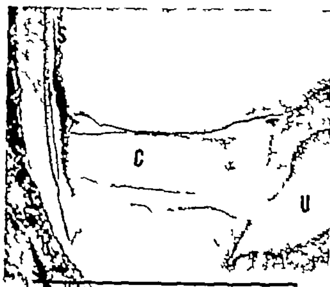


Fig. 7 Left ear from 6 month bilaterally deaf white cat showing saccule (*S*), utricle (*U*) and the "cyst" formation (*C*) in the postero-superior corner of the saccular lumen Marker = 1 *mm*.

or juxta-utricular pole of the saccule. Commencing degeneration of the supporting cells is evident and in some areas towards the anterior pole the layer of supporting cells is patchily absent. The uniform layer of eosinophilic precipitate found in the previous age group is now broken up into localised accumulations of a more deeply eosinophilic material A definite layer is found only at the posterior pole where sensory cells can still be identified

At twenty-one months further reduction in sensory cell numbers has occurred and there is little eosinophilic precipitate remaining. A very few sensory cells remain at the postero-superior corner of the macula. In the eight year-old adult (Fig. 6 F) the layer of deeply basophilic staining otoconia persists, apparently unchanged and remains enclosed in the cellular membrane. No sensory cells can be identified and the supporting cells are markedly degenerated the cell borders cannot be identified and the nuclei are pyknotic. There are many areas, especially towards the anterior pole where also the supporting cells are absent

Both the obliteration of the saccular lumen and the subsequent degeneration of the macula first of the sensory cells and at a later stage, of the supporting cells, commence at the anterior or cochlear pole of the saccule and extend successively in a posterior direction The posterior or juxta utricular part of the saccular lumen is, however never obliterated A constant feature which first makes its appearance at day twenty and thereafter persists throughout life is the appearance of a cyst-like formation in the postero-superior corner of the saccular lumen. A typical "cyst from a six month deaf cat is shown in Fig. 7 None of the hearing ears presented this finding. Study of consecutive sections has shown that the cyst" is formed by a herniation medially and superiorly of the lateral saccular wall into the patent postero-superior corner of the saccular lumen The structure is therefore cone shaped and communicates laterally and inferiorly with the perilymphatic space of the vestibule. Considerable variation in size was found the largest having a vertical height of 220 microns and the smallest about 60 microns. The size of the cyst" was not related to the age of the animal None of the specimens showed defects in the cyst" wall which would permit admixture of perilymph and endolymph and no adhesions were found between the "cyst" walls and the inner aspect of the saccule

The utriculosaccular duct and the ductus endolymphaticus were patent in all pathological ears The endolymphatic sac contained a variable amount of deeply eosinophilic staining material but the picture was inconstant. A ten month animal with unilateral degeneration showed considerable precipitate, especially in the rugose portion of the sac, but the amount and the staining characteristics were similar in both ears. In the deaf adult animals the amount of precipitate varied from slight through moderate to considerable No otoconia were found in the endolymphatic duct or sac and there were no significant differences in the dimensions of the vestibular aqueduct and endolymphatic ducts of pathological and normal ears. The lumen of the ductus reuniens was markedly reduced and often obliterated in the older pathological ears.

No differences were found in the amount or distribution of pigment in the vestibular labyrinth in the three groups studied for this pur



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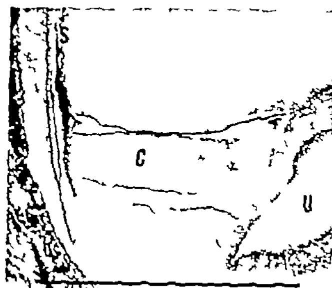


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encapsulation It is tempting to regard this encapsulation as a protective response of the organism to injury Deol & Lane 1966 have presented evidence which would suggest that the otoliths are secreted by the maculae. If this hypothesis is correct, the presence of an histologically normal otolithic layer at the eight day stage would indicate that at least part of the macula has been capable of normal function prior to that date.

The waltzer-shaker group of mouse mutants has been classified into two groups on the basis of differences in the time course of the labyrinthine degeneration (Grüneberg, 1955) In the morphogenetic group the labyrinth shows gross structural abnormalities which must have occurred at an early stage of embryogenesis. The development of the labyrinth in the second, degenerative, group proceeds normally up to, and for a variable time interval subsequent to birth before degeneration occurs. Ormerod (1960) considered that the Scheibe type of abnormality represented a degenerative effect, but Deol (1968) disagreed with this view The light microscopical evidence from the white cat favours the former hypothesis, but it is probable that electron microscopy would reveal structural changes at an even earlier date (Ernstson et al., 1969)

The acoustic ganglion has been shown to arise, at least in part, from the neural crest (Deol, 1967) and inner ear abnormalities have been regarded as an expression of genetically determined abnormalities in the latter structure The finding of cells morphologically similar to Scarpa ganglion cells in the saccular macula may be indicative of anomalous innervation of the end-organ at an early stage in development. The absence of ganglion cell loss in the saccular division of Scarpa's ganglion is in marked *contrast to the* situation found in the spiral ganglion of the deaf white cat (Mair IV)

In the mouse a high degree of correlation has been found between the extent of hereditary inner ear degeneration and the distribution of pigment in the labyrinth (Deol, 1970). In addition, the two ears of individual animals often showed asymmetrical degeneration of both the cochlea and the saccule The situation in the white cat would appear to be completely different. In animals with bilateral hearing loss the saccular degeneration was symmetrical at all stages, and no correlation could be found between the presence of cochleo-saccular degeneration and the amount or distribution of pigment in the membranous vestibular labyrinth. Bilateral symmetry also characterises the cochlear (Mair III) and the spiral ganglion (Mair IV) degenerations in the bilaterally deaf white cat.

ZUSAMMENFASSUNG

Eine elektronystagmographische Untersuchung der Vestibularfunktion bei tauben weissen Katzen ergab keine funktionellen Anomalitäten Histologische Veränderungen wurden im Sacculus nachgewiesen und waren als Funktion des zunehmenden Alters stärker ausgeprägt. Einem Kollaps der Sacculus-Wand folgte ein Einkapselung der otolithischen Membran In allen Stadien der degenerativen Prozesses war der Kochlea am nächsten liegende Abschnitt des Sacculus stärker betroffen als die weiter dorsal gelegenen Bereiche. Die degenerativen Veränderungen dehnen sich strahlenförmig vom Ductus reuniens aus und zeigen keine Korrelation zum Ausmass der Innenohr Pigmentierung

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gressively greater in the more posterior parts of the saccule This contrasts with the report of more severe hair cell degeneration in the posterior part of the macula sacculi in three species of dog with hereditary cochleo-saccular degeneration (Igarashi et al 1972) Cochlear degeneration in the deaf white cat is also characterised by unequal rates of degeneration the basal coil being affected first and the apical last (Mair III) Cochleo-saccular degeneration in the deaf white cat would therefore appear to develop centrifugally from the region of the ductus reuniens

The important stages of the inner ear degeneration in the deaf white cat have been previously reported to be virtually complete by the twenty first day (Bosher & Hallpike 1965) The present study confirms that the volume changes in the saccule with near obliteration of the lumen, are fully advanced by day twenty but significant sensory cell loss does not occur until later between day twenty six and day forty three and loss of supporting cells is not evident until after six months The degenerative process is a continuous one and apparently persists throughout life there being a marked difference in the extent of macular cell loss between the four year and the eight year deaf adult animals. In contrast to previous reports (Wilson & Kane 1959 Suga & Hattler 1970) a normal saccule was never found in deaf ears.

The finding of a normal pars superior in the presence of almost complete obliteration of the cochlear and saccular endolymphatic spaces supports the contention of Schuhneckt & McNeil (1966) that the sources of endolymph production are independent in the phylogenetically different parts of the labyrinth Obliteration of the saccular lumen is however not complete the posterior part remaining patent in all cases a finding which has been previously noted by Bosher & Hallpike (1965) There are however no other reports in the literature of the peculiar infolding of the postero-lateral saccular wall which produced the "cyst" formation found in all the pathological ears The significance of this finding is at present unclear but the infolding was definitely not produced by adhesions and may therefore be an expression of unequal pressure gradients on the opposing sides of the saccular wall Perlman (1940) described a reenforced area in the anterior part of the lateral saccular wall in the human labyrinth and demonstrated that the more posterior areas were more susceptible to pressure changes. However since this reenforcement was not present in lower animals, including the cat, the explanation of the "cyst" formation must be sought elsewhere

Defects in the saccular wall, similar to those described in the deaf Hedlund white mink (Sugiura & Hilding, 1970) were not found Rupture of the saccular wall with admixture of perilymph and endolymph is therefore not an aetiological factor in the development of the degenerative process in the deaf white cat. The utriculo-endolymphatic valve was intact in all specimens and it is therefore possible that the fluid presumably endolymph, present in the patent posterior part of the saccule was derived from the endolymphatic duct or sac (Seymour 1960).

Envelopment of the retracted tectorial membrane by a layer of flattened cells has been frequently reported in studies of human and animal deafness (Ward et al 1962 Suga & Hattler 1970) but reports of a similar process in the saccule are rare Myers et al (1971) found the saccular otolithic membrane completely encased in a fibrous tissue envelope in the temporal bones of a seven day old boy with the syndrome of deafness spiny hyperkeratosis and universal alopecia. A similar process has also been reported in measles virus labyrinthitis (Lindsay & Hemenway 1954) No other reports were found in the literature

In this series of deaf white cats the saccular otoliths were first surrounded by a layer of flattened cells at the twelve day stage, and this cellular response increased as a function of age Little change occurred in the otoconia between twenty days and eight years of age Quantitative increase of the saccular otoliths with subsequent fragmentation and scattering of the layer have been described in the mouse (Deol 1970) where as the response in the cat is confined to an early increase in size of the individual otoconia with

III Cochlear Histopathology

Abstract The degeneration process in the cochlea of the hereditarily deaf white cat was studied in different age groups and the early stages compared with the postnatal morphological maturation in the hearing animal. Both processes commence in the upper half of the basal coil and extend longitudinally along the duct. Obliteration of the cochlear duct and degeneration of the stria vascularis are prominent early features, but no hydrops was found. A radial progression across the basilar membrane also occurs, the outer hair cells degenerating before the inner. A conspicuous feature, which is first found in the twelve day deaf animal, is the appearance of discrete, homogeneous spheres in the tectorial membrane. These structures appear to emanate from the region of the inner dental cells.

Deafness which is present at or soon after birth may have either an acquired or a hereditary aetiology. The histopathological findings in human congenital deafness have been reviewed by Ormerod (1960) and classified into two major groups: those cases in which there is a serious under- or maldevelopment of the inner ear, and a second group in which degenerative changes occur in the end organ at a later stage of development.

The most frequent temporal bone finding in the former developmental or morphogenetic group, is the Mondini type of aplasia with, *inter alia*, anomalies of the osseous labyrinth framework (Altmann, 1950; Beal et al. 1967). A developmental aetiology can often be assumed in those ears in which malformations of the membraneous labyrinth are associated either with abnormalities of the bony labyrinth or with atresia of the external meatus (Altmann, 1950). Further differential diagnostic information is provided by the presence of associated anomalies as in the Arnold–Chiari malformation (Altmann, 1964) and the trisomy syndromes (Kos et al. 1966). However developmental disorders at an early stage in embryogenesis are not necessarily synonymous with a hereditary aetiology.

The situation with respect to the second group of degenerative or regressive changes in the labyrinth is even more uncertain. Here, the Scheibe or cochleo-saccular type of degeneration is the most common (Altmann 1950; Ormerod, 1960), but similar temporal bone findings have been reported in hereditary deafness (Fisch, 1959), in deafness due to viral infection (Lindsay & Hemenway 1954) and in presbycusis (Schuknecht et al., 1965) in human material. The difficulties in deciding whether deafness in the individual case is hereditary or acquired are often insurmountable (Beal et al. 1967; Lindsay & Matz, 1968).

Human studies are hampered by the comparative dearth of histological material and by the impossibility of genetically controlled investigations. These factors do not apply to animal studies and, fortunately, many species present hereditary disorders of the labyrinth, some of which are histologically similar to presumed hereditary deafness in man. Particular attention has been paid to the hereditary inner ear degeneration of the various mouse mutants in the waltzer–shaker group. These mutants have also been classified into a morphogenetic group, in which gross abnormalities of the labyrinth arise at an early stage in development, and a degenerative group, where the gross structure of the labyrinth is normal at birth, but degenerative changes appear in the neuroepithelia at a variable period thereafter and are usually progressive (Grüneberg, 1955). The cochleae of these latter mutants present to a varying degree a degeneration of the organ of Corti, the stria vascularis and the spiral ganglion. In several mutants the cochlear changes are accompanied by a progressive degeneration of the saccular macula (Deol, 1968), i.e. Scheibe type, whereas in others

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the sensory structures of the pars superior are affected to a varying degree (Deol 1954)

In 1910 van Lennep showed that the inner ear of the Japanese waltzing mouse was morphologically normal at birth and that the structural changes did not develop until ten days post partum, being thereafter progressive with age The time course of the inner ear degeneration has since been established for a great variety of mouse mutants (Deol 1968) Other species which have been extensively studied are the Hedlund white mink (Sugiura & Hilding, 1970) and the waltzing guinea pig (Ernstson 1971)

Although the literature on hereditary hearing loss contains many detailed descriptions of the time course of the cochlear degeneration in rodents, there are few comparable studies in the hereditarily deaf white cat Degeneration of the organ of Corti with collapse of the cochlear duct was first observed in the deaf white cat at the turn of the century (Rawitz, 1897 Alexander 1900) and this picture of the late stages of the degenerative process has since been confirmed by several investigators (Wilson & Kane, 1959 Suga & Hattler 1970) The different stages in the development of the cochlear end organ degeneration in the deaf white cat have been previously described only once in any detail in the literature (Bosher & Hallpike 1965) The current report presents the cochlear histopathological findings from a larger series of deaf animals studied over a longer survival period with emphasis on some important features which have not previously been described.

MATERIAL AND METHODS

A white cat stock of ninety-six animals was gradually acquired over a period of time Details of this population have been given previously (Mair I) Cochlear potential measurements from a round window electrode were performed bilaterally in all 96 animals and in a control group of 54 colour coat kittens and adult cats. The presence or absence of hearing was unequivocally established for all animals over seven days of age Bilateral hearing loss was found in 26 and unilateral in 8 of the white coat animals. All colour coat animals from the experimental stock and all 54 of the control group had cochlear potentials within the range of normal for the respective age groups Both the coloured and white coat populations were sacrificed at varying intervals after birth by the standard method of intravital cardiac perfusion using Heidenhain s Susa solution as fixative Survival periods varied from the first postnatal day up to eight years of age The temporal bones and hind brains were removed in separate blocks in the majority of animals, and in all cases were processed for light microscopy The temporal bones were imbedded in celloidin with the mid modiolar axis of the cochlea orientated in the horizontal plane. Serial sections were cut at a thickness of 20 microns and every tenth and in many ears fifth section was stained with haematoxylin and eosin

The important early stages of the degenerative process in the deaf white cat were compared with the normal postnatal maturation of the cochlea in colour coat animals. A quantitative estimation of the latter was obtained by measurements of the organ of Corti in five selected age groups of kittens and hearing adult cats. Mid modiolar sections were studied and measurements made in the upper half of each coil using a micrometer eye piece attachment. The height of the open tunnel of Corti was measured as the perpendicular from the upper surface of the basilar membrane to the contact point of the pillars. Hair cell length was taken as the distance along the long axis from the base of the cell to the mid point of the diagonally inclined cuticular plate The greatest transverse diameter of the hair cell at the level of the nucleus was measured to represent the width. Measurements were not practicable in the hook region on account of the angle of section The postnatal development of the normal cochlear duct and of the degenerative process in the cochlea of the deaf white cat were studied in progressively older age groups and in all coils of the cochlea.

Table 10. *Tunnel of Corti, mean height in microns and standard deviation* ($n=6$) *of open tunnel in different postnatal age groups of colour coat animals*

Age in days	Height		
	Coil 1	Coil 2	Coil 3
1	13.4±10.45	0	0
5	27.1±2.47	0	0
8	33.5±3.50	34.5±6.37	0
10	38.4±2.37	44.5±3.68	39.0±5.43
30	39.5±1.68	44.8±1.79	42.9+2.37
Adult	40.4±1.02	45.0±1.58	45.1±1.67

RESULTS

1. *Postnatal development in normal colour coat stock*

The postnatal morphological maturation of the organ of Corti in colour coat stock was found to commence in the upper half of the basal coil and to extend longitudinally along the cochlear duct from this site. The dimensions of the open tunnel of Corti and of the inner and outer hair cells of colour coat animals are shown in Tables 10–12 for five age groups of kittens, aged from one to thirty days, and for adult animals. Opening of the tunnel and histological maturation of the outer hair cells occurred at approximately the tenth day in the hook region, but the angle of section did not permit a more accurate assessment. Table 10 demonstrates that the tunnel is patent only in coil one at the fifth day, opens first in coil two at day eight and at the apex by the tenth postnatal day. The dimensions of the inner hair cells do not change significantly from the first postnatal day to the adult stage in any of the coils (Table 11). On the other hand, maturation results in a striking change in the configuration of the external hair cells (Table 12). In the newborn these cells are short and wide, whereas in the mature cochlea they are long and slender. This process parallels the opening of Corti's tunnel. Thinning and elongation of the outer hair cells have occurred by day five in the first coil, by day eight in coil two and by the tenth day in the apical coil.

2. *Pathological material*

No abnormalities were found in the osseous cochlear framework in the sixty deaf ears from the white cat stock. Pathological changes were confined to the structures of the membranous cochlear duct and the spiral ganglion. The latter will be described in a succeeding publication. The first light microscopical sign of a departure from the normal course of postnatal maturation was found at day eight, and consisted of a wavy appearance of Reissner's membrane in the upper half of coil one. Two days later, at day ten, Reissner's membrane is in contact with the inner limbal zone of the tectorial membrane in the first coil (Fig. 9 Medea). At this stage the light microscopical appearances of Corti's organ in hearing and deaf animals are almost indistinguishable (Fig. 9 Kit 18 & Medea). At day twelve the dimensions of the cochlear duct are further reduced and Reissner's membrane is now in contact with the spiral prominence although the lumen is still patent above and below the

Table 11. *Inner hair cells, mean width and length in microns and standard deviation* ($n=6$) *in different postnatal age groups of colour coat animals*

Age in days	Width			Length		
	Coil 1	Coil	Coil 3	Coil 1	Coil 2	Coil 3
1	11.7±1.66	12.0+0.63	11.3_1.58	31.8±1.97	30.6±2.32	30.5±4.01
5	12.7±1.71	11.9+0.93	11.4_0.84	30.4±1.72	30.8±1.14	29.5±1.56
8	10.4 1.16	10.9 0.90	10.3±1.05	27.4±1.47	30.9±2.70	31.3±2.34
10	10.8 0.32	11.3_0.84	10.4±0.39	28.2±2.20	32.6±2.28	31.3±1.25
30	11.8±0.92	11.9 0.64	11.8±0.74	29.4±1.22	30.0±0.55	31.3+2.13
Adult	10.5 0.29	11.0_1.34	10.7±1.01	29.3±1.32	30.4±1.20	30.1±2.06

the sensory structures of the pars superior are affected to a varying degree (Deol 1954)

In 1910, van Lennep showed that the inner ear of the Japanese waltzing mouse was morphologically normal at birth and that the structural changes did not develop until ten days post partum being thereafter progressive with age The time course of the inner ear degeneration has since been established for a great variety of mouse mutants (Deol 1968) Other species which have been extensively studied are the Hedlund white mink (Sugiura & Hilding, 1970) and the waltzing guinea pig (Ernstson 1971)

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The important early stages of the degenerative process in the deaf white cat were compared with the normal postnatal maturation of the cochlea in colour coat animals. A quantitative estimation of the latter was obtained by measurements of the organ of Corti in five selected age groups of kittens and hearing adult cats. Mid modiolar sections were studied and measurements made in the upper half of each coil using a micrometer eye piece attachment. The height of the open tunnel of Corti was measured as the perpendicular from the upper surface of the basilar membrane to the contact point of the pillars. Hair cell length was taken as the distance along the long axis from the base of the cell to the mid point of the diagonally inclined cuticular plate. The greatest transverse diameter of the hair cell at the level of the nucleus was measured to represent the width. Measurements were not practicable in the hook region on account of the angle of section The postnatal development of the normal cochlear duct and of the degenerative process in the cochlea of the deaf white cat were studied in progressively older age groups and in all coils of the cochlea

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Age in days	Width			Length		
	Coil 1	Coil 2	Coil 3	Coil 1	Coil 2	Coil 3
1	11.7 ± 1.66	1[illegible]0 ± 0.63	11.3 ± 1.50	31.8 ± 1.97	30.6 ± 2.32	30.5 ± 4.01
5	12.7 ± 1.71	11.9 ± 0.93	11.4 ± 0.84	30.4 ± 1.72	30.8 ± 1.14	29.5 ± 1.36
8	10.4 ± 1.16	10.9 ± 0.90	10.5 ± 1.05	27.4 ± 1.47	30.9 ± 2.70	31.3 ± 2.34
10	10.8 ± 0.32	11.3 ± 0.84	10.4 ± 0.39	33.2 ± 2.20	32.6 ± 2.38	31.3 ± 1.25
30	11.8 ± 0.92	11.9 ± 0.64	11.8 ± 0.74	29.4 ± 1.22	30.0 ± 0.55	31.3 ± 2.13
Adult	10.5 ± 0.25	11.0 ± 1.34	10.7 ± 1.01	29.3 ± 1.52	30.4 ± 1.20	30.1 ± [illegible].06

Table 12. *Outer hair cells mean width and length in microns and standard deviation (n = 6) in different postnatal age groups of colour coat animals*

Age in days	Width			Length		
	Coil 1	Coil 2	Coil 3	Coil 1	Coil 2	Coil 3
Inner row						
1	10.6±1.43	12.3±0.98	12.6±1.53	18.2±1.14	19.0±[illegible].32	19.[illegible]±[illegible].50
5	8.7±1.42	12.8±0.77	1[illegible].5±0.51	17.5±1.38	18.3±0.81	18.8±1.63
8	7.8±1.19	7.8±1.79	12.9±1.55	21.7±[illegible].28	25.1±2.74	16.0±1.75
10	5.7±1.20	6.3±1.43	7.0±0.75	24.3±4.09	30.1±2.72	25.9±1.07
30	6.0±0.46	6.3±0.50	6.4±0.64	[illegible]3.3±2.45	29.8±1.80	37.[illegible]±3.68
Adult	6.4±0.33	6.8±0.25	6.8±0.46	23.0±2.04	[illegible]8.5±1.96	35.4±1.57
Middle row						
1	10.8±1.00	11.8±1.80	11.7±1.19	18.[illegible]±0.63	18.7±0.75	19.7±2.40
5	7.4±1.47	12.9±0.46	12.6±0.63	17.9±1.14	17.0±0.90	17.4±0.93
8	6.7±1.28	7.8±2.43	12.3±1.83	23.3±1.69	[illegible]5.9±2.99	15.5±1.63
10	5.3±1.00	6.1±0.95	6.6±0.60	25.[illegible]±2.91	30.5±1.52	28.8±[illegible].95
30	5.8±0.33	6.3±0.50	6.9±0.50	24.4±1.19	35.1±[illegible].37	40.3±5.00
Adult	6.5±0.3	6.8±0.46	7.4±0.46	23.4±3.03	30.8±[illegible]	36.1±2.15
Outer row						
1	10.7±0.84	11.6±1.69	10.7±1.27	16.9±1.32	17.4±1.63	17.9±[illegible].11
5	6.8±0.98	12.4±0.50	12.3±1.31	18.9±1.79	15.3±0.77	15.6±1.33
8	5.1±0.32	7.5±2.56	11.7±1.91	23.7±2.70	23.5±3.16	14.5±2.13
10	4.4±0.71	5.2±0.64	6.8±0.90	26.3±2.92	29.8±[illegible].37	[illegible]7.3±[illegible]
30	5.8±0.51	6.1±0.39	7.1±0.50	[illegible]6.6±3.21	37.5±2.61	40.2±4.65
Adult	6.4±0.33	6.6±0.46	7.3±0.55	23.5±2.56	32.6±[illegible].04	35.5±2.71

prominence and above Corti's organ (Fig. 9 Astyanax). *Further development consists of an* increasingly greater reduction of the cochlear lumen, with finally adhesion between Reissner's membrane on the one hand and the stria vascularis and degenerated Corti's organ on the other (Fig. 9 Romeo). These changes commence in the upper half of the basal coil and extend longitudinally along the cochlear duct from basal to apical coils and also towards the round window there being a time delay of approximately one to two days between coils one and two and a similar interval between the second and the apical coils. This regular sequential progression is a constant feature of the degenerative process for all structures of the cochlear duct, although the time intervals vary considerably.

The cochlear duct volume was reduced in all ears with absent round window potentials. In none of the deaf ears was a hydrops found.

The degeneration process commences almost simultaneously in the pillars and hair cells, but the first signs are not visible until after Reissner's membrane has commenced to descend towards the stria and the basilar membrane. These structural changes are first found in coil one, appear consecutively later in the upper coils and the hook region, and consist of a collapse of the rods, hair cells and supporting cells towards the modiolus with subsequent degeneration of all cellular components of Corti's organ.

At day ten the rods of Corti are erect and the tunnel patent in the basal coil (Fig. 10 Medea). At the twelfth day the pillars have collapsed towards the modiolus (Fig. 10 Astyanax). This process proceeds rapidly and one week later there is very little tunnel lumen visible in the second coil, whereas in coil three the tunnel is still patent and the pillar cells erect. Pillar cells can be identified in coil one at day fifty-three (Fig. 10 Upsilon) but by six months have degenerated completely (Fig. 10 Andromache). At fourteen months no tunnel lumen can be identified in any coil and only the inner pillar cells are distinguishable in coils two and three. During the second year the inner pillars are still present,

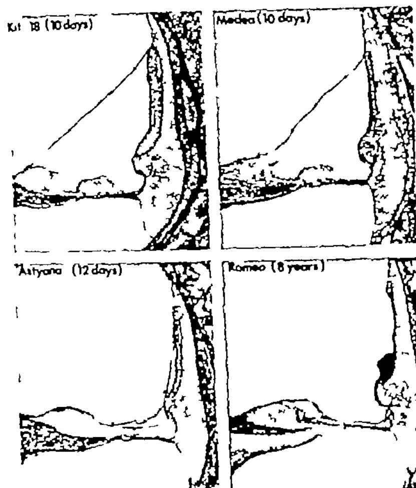


Fig. 9. Sections of the cochlear duct from the upper half of the basal coils. Kit 18: histologically mature Corti's organ from a ten day colour coat kitten. Medea, ten day deaf white cat: Reissner's membrane has an irregular wavy appearance and the stria vascularis is thinner than in the hearing animal. Astyanax: twelve day deaf white cat showing marked reduction of the endolymphatic space and collapse of Corti's organ. Romeo: eight year deaf white cat. There is total disappearance of Corti's organ, atrophy of the stria and considerable precipitate accumulation above the spiral prominence.

although deformed, in coil three, but after two years of age no pillars can be recognised in any coil.

A similar process is found in the hair cells, both inner and outer. Prior to the tenth day the cochlear development in the deaf white cat consists of a gradual histological maturation similar to that found in hearing animals. The tunnel opens, the outer hair cells lose their foetal appearance, become longer and thinner and the extracellular spaces appear. At day ten the cytoplasm of the hair cells presents a granular appearance (Fig. 10, Medea). From day twelve onwards the hair cells accompany the pillars and collapse towards the modiolus (Fig. 10, Astyanax), first in coil one and subsequently in the upper coils. In the outer hair cells degeneration of the third row always occurs before rows one and two. Degeneration of the inner hair cells occurs at a somewhat later date than in the outer in all coils, and this interval is on the average two to four months. At day twenty the cell outlines of the outer hair cells in coil one can be identified only with difficulty and at day fifty-three all

Table 12. *Outer hair cells mean width and length in microns and standard deviation (n = 6) in different postnatal age groups of colour coat animals*

Age in days	Width			Length		
	Coil 1	Coil 2	Coil 3	Coil 1	Coil 2	Coil 3
Inner row						
1	10.6±1.43	12.3±0.98	12.6±1.53	18.[illegible]±1.14	19.0±2.32	19.2±2.50
5	8.7±1.42	12.8±0.77	12.5±0.51	17.5±1.38	18.3±0.81	18.8±1.63
8	7.8±1.19	7.8±1.79	12.9±1.55	21.7±2.28	25.1±2.74	16.0±1.75
10	5.7±1.20	6.3±1.43	7.0±0.75	24.3±4.09	30.1±2.72	25.9±1.07
30	6.0±0.46	6.3±0.50	6.4±0.64	[illegible]3.3±2.45	[illegible]9.8±1.80	37.2±3.68
Adult	6.4±0.33	6.8±0.[illegible]5	6.8±0.46	[illegible]3.0±2.04	[illegible]8.5±1.96	35.4±1.57
Middle row						
1	10.8±1.00	11.8±1.80	11.7±1.19	18.2±0.63	18.7±0.75	19.7±2.40
5	7.4±1.47	12.9±0.46	12.6±0.63	17.9±1.14	17.0±0.90	17.4±0.93
8	6.7±1.28	7.8±2.43	12.3±1.83	23.3±1.69	25.9±2.99	15.5±1.63
10	5.3±1.00	6.1±0.95	6.6±0.60	25.2±2.91	30.5±1.52	[illegible]8.8±[illegible]95
30	5.8±0.33	6.3±0.50	6.9±0.50	24.4±1.19	35.1±2.37	40.3±5.00
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1	10.7±0.84	11.6±1.69	10.7±1.27	16.9±1.32	17.4±1.63	17.9±[illegible]11
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8	5.1±0.32	7.5±2.56	11.7±1.91	23.7±2.70	23.5±3.16	14.5±2.13
10	4.4±0.71	5.2±0.64	6.8±0.90	26.3±2.92	[illegible]9.8±[illegible]37	27.3±2.89
30	5.8±0.51	6.1±0.39	7.1±0.50	26.6±3.21	37.5±2.61	40.[illegible]±4.65
Adult	6.4±0.33	6.6±0.46	7.3±0.55	23.5±2.56	3[illegible].6±2.04	35.5±[illegible]71

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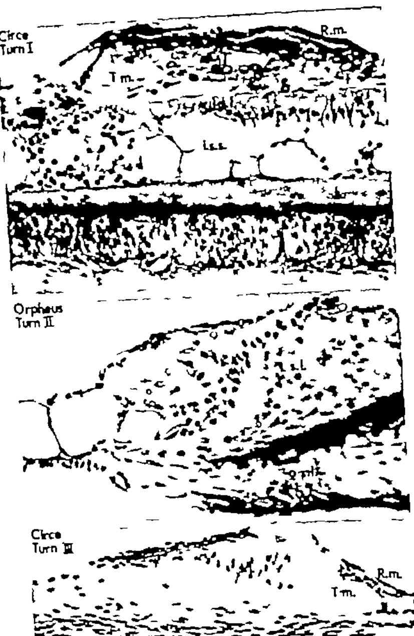


Fig. 11. Sections showing the varying appearance of the tectorial membrane and the blue-grey spheres in deaf animals. Abbreviations: T.m. Tectorial membrane; R.m. Reissner' membrane; l. spiral limbus; l. l. vesicular lip of the spiral limbus; o.s.l. osseous spiral lamina; i.s.s. inner spiral sulcus. Upper: basal half of coil one from 28 month deaf animal. A prominent feature of the vestibular lip is the row of Huschke's teeth with the interdental furrow containing the nuclei of the interdental cells. The tectorial membrane is covered on its upper surface by Reissner' membrane. Scattered throughout the former are numerous, spherical or elongated structures (arrows) which have an homogeneous appearance. Middle: second coil of 14 month deaf animal. The tectorial membrane is rolled up in the inner spiral sulcus and the spheres are prominent in the membrane and can also be traced along the upper surface of the vestibular lip. Lower: third coil of 28 month animal. No spheres are visible in this section of the tectorial membrane, but numerous elongated structures with the same staining characteristics are present on the upper surface of the vestibular lip (arrow).

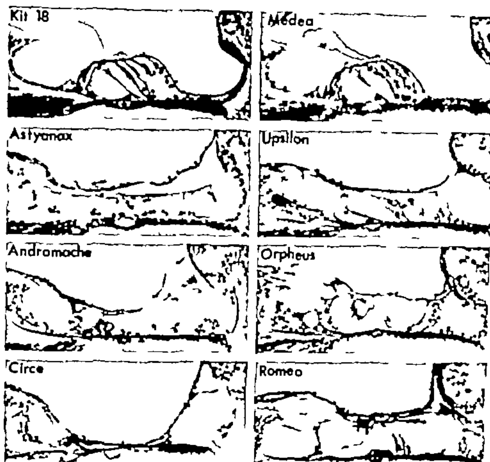


Fig 10 Higher power views of Corti's organ from the upper half of the basal coils. Kit 18 mature Corti's organ from ten day colour coat kitten. Medea, ten day deaf animal. Reissner's membrane has commenced to descend towards the tectorial membrane and the external hair and Deiter's cells have a granular appearance of the cytoplasm. Corti's tunnel is patent and the upper tunnel radial fibres are visible. Astyanax twelve day deaf animal. Reissner's membrane is in contact with the spiral prominence and covers the still elongated tectorial membrane. The pillar cells, hair and supporting cells have collapsed towards the modiolus, and large cystic spaces are found in the external sulcus cells. The vessel of the basilar membrane is large and patent. Upsilon fifty three day deaf animal. The tectorial membrane has retracted into the inner spiral sulcus and the pillar cells can be identified although deformed. The hair cells are degenerated and the cystic spaces in the outer sulcus cells have coalesced. Andromache six month deaf animal. The pillar cells are no longer identifiable and Corti's organ is replaced by undifferentiated cells. Further stages of this process are shown in the fourteen month (Orpheus), the twenty-eight month (Circe) and the eight year old adult (Romeo)

outer hair cell outlines are obliterated in this coil (Fig. 10 Upsilon) At this stage the first row of outer hair cells in coil two and all three rows in coil three are still distinguishable. Both inner and outer hair cells can be identified in the hook region at day fifty three Inner hair cells are first consistently absent in coil one at the ten month stage Increasing hair cell loss occurs in the first and second years (Fig 10 Andromache & Orpheus) and at twenty-two months no outer hair cells can be recognised although the inner hair cells are still present at the apex and towards the round window At twenty-eight months no inner hair cells can be identified throughout the cochlear duct. Hair cells are entirely absent in the adult.

The cells of Deiters and Hensen accompany the pillars and hair cells when the latter collapse towards the modiolus and can still be identified up to the end of the second month in the upper coils but thereafter further degeneration occurs No basal migration of the Deiters cell nuclei was observed The end result is a complete loss of cellular identity with either disappearance of Corti's organ, in which case Reissner's membrane lies in contact with the denuded basilar

coils and becomes covered with a monocellular sheath. The blue-grey spheres are a constant feature of all deaf ears after day twelve. They increase in size and number with age in the first two coils, but in coil three they remain small although becoming more numerous in the older age groups (Fig. 11). The spheres are sparse in the hook region, but persist throughout the tectoral membrane apparently unchanged, even in the eight year deaf adult. Discrete, elongated structures, with staining characteristics similar to the spheres, can be traced along the vestibular lip between the spiral limbus and the tectorial membrane towards the region of the interdental cells (Fig. 11). None of the hearing ears presented this finding.

The stria vascularis of the deaf white cat is indistinguishable at day eight from that of the hearing animal (Fig. 12 A). At this stage the stria is well developed, especially the deep reticulated layer has an irregular surface in all coils and contains many capillaries. At day ten the surface of the stria in coil one is smoothed out (Fig. 12 B) and the stria appears thinner than in the ten day hearing animal (Fig. 12 A). Two days later this surface change has extended to coil two and the spiral prominence of the first coil is now paler where Reissner's membrane is in contact (Fig. 12 C). The stria subsequently becomes thinner and there is a progressive obliteration of the vascular spaces (Fig. 12 D–H). In the adult this process has progressed until the combined Reissner's membrane and stria are only one cell thick at the upper peripheral angle of the duct (Fig. 12 H). Above the spiral prominence there appears in some sections a deeply eosinophilic staining precipitate which increases in quantity with age.

The external sulcus cells appear unremarkable in the ten day deaf animal (Fig. 10 Medea). Two days later these cells have increased greatly in size and the cytoplasm is paler and vacuolar with formation of large cystic spaces (Fig. 10, Astyanax). By day twenty the cystic spaces have increased further in size in all coils, and the nuclei appear pale with an irregular outline. With increasing age the nuclei become more pyknotic (Fig. 10, Upsilon), the cystic spaces smaller and precipitate accumulates, eosinophilic beneath the spiral prominence and basophilic in the angle between the basilar membrane and spiral ligament. The latter presents an increasing pallor due to cell loss with advancing age, but no change is apparent in the basilar membrane. Degeneration with ultimate disappearance is also found in the inner sulcus cells, but without the formation of cystic spaces (Fig. 10).

The vessel of the basilar membrane (vas spirale) is present in all age groups, although considerably larger in the younger animals (Fig. 10). In many sections this vessel gives the appearance of being occluded by an amorphous, lightly basophilic staining material, but in the oldest, eight ear deaf animal erythrocytes were visible in the vessel lumen in the basal coil (Fig. 10, Romeo). The cochlear vascular system was otherwise unremarkable.

The inner ear degeneration was strikingly symmetrical in both ears of bilaterally deaf animals irrespective of age. The end result of this process of degeneration of the cochlear structures in the aged adult is shown in Fig. 9 Romeo with obliteration of the endolymphatic space, complete disappearance of all components of Corti's organ and degeneration of the stria vascularis.

DISCUSSION

Numerous morphological and physiological studies have shown that the cochlea of the newborn mammal is immature in many species, and that a rapid and systematic development occurs in the early postnatal period. The majority of investigators have demonstrated that the maturation process spreads sequentially along the cochlear duct from basal to apical coil (Deol, 1954; Ånggård, 1965). The present study of the colour coat stock confirms that histological maturation of the cat cochlea comences in the upper half of the basal coil and extends longitudinally along the cochlear duct, both apically towards the helicotrema and basally towards the round window. The reported tunnel and hair cell meas-

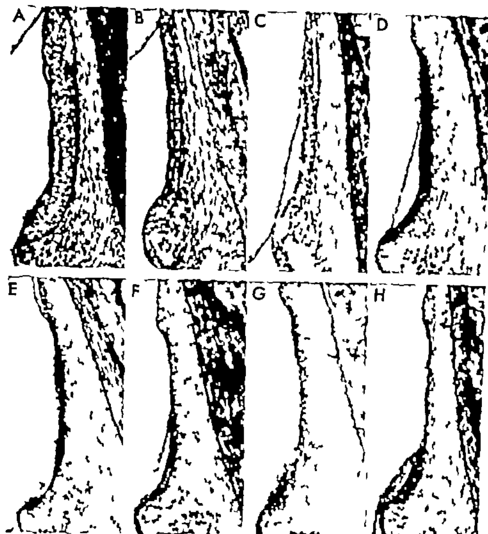


Fig 12 The stria vascularis, spiral prominence and spiral ligament from the upper half of the basal coil in different age groups. (A) 10 day hearing animal (B) 10 day deaf white cat. The stria is thinner than in A and the surface has a smoother appearance. (C) 12 day deaf animal. Reissner's membrane is in contact with the upper part of the stria and the spiral prominence. The latter appears paler but the stria still contains numerous vascular spaces. (D) 53 day deaf animal. The stria is more deeply staining, cell outlines are largely obliterated and the vascular spaces reduced considerably in diameter (E) 6 month deaf animal The degenerated stria and Reissner's membrane have coalesced There is marked cell loss in the stria and absence of vascular spaces. Further stages are shown in the fourteen month (F), approximately three year (G) and the eight year (H) adult animals. There is progressive cell loss in the stria until the combined stria and Reissner's membrane constitute a monocellular layer (H)

membrane (Fig. 10, Circe) or else persistence of some degenerated cells with fibrous adhesions between the two membranes (Fig 10 Romeo) Both of these end stages can usually be found at different sites in the same ear

The tectorial membrane at day ten is in its limbal zone in contact with Reissner's membrane due to the descent of the latter towards the basilar membrane Two days later almost the entire upper surface of the tectorial membrane is covered by the closely applied Reissner's membrane (Fig 10 Astyanax) The former is, however still elongated and in contact with Corti's organ Small, grey blue spheres are visible at day twelve along the undersurface of the tectorial membrane in coil one, and to a lesser extent in coil two One week later the tectorial membrane has retracted towards the inner sulcus and presents a rolled up globular appearance in the first coil This appearance is less marked in coil two and at the apex the membrane is still elongated and covering the persisting Corti's organ The membrane subsequently retracts towards the modiolus in all

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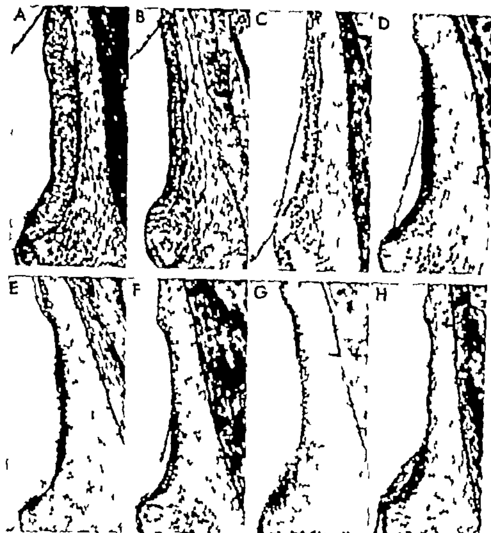


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of hereditary degeneration in the youngest cells of the cochlea may be a manifestation of a similar difference in susceptibility. In this context it is perhaps noteworthy that the basal coil is also more susceptible to damage in ototoxicity (Benitez et al. 1962), in presbycusis (Schuknecht et al. 1965) and in viral labyrinthitis (Lindsay & Hemenway 1954).

Many theories as to the pathogenesis of the inner ear degeneration in the deaf white cat have centered around disorders of endolymph production (Wilson & Kane, 1959; Bosher & Hallpike, 1965). The latter authors stressed the importance of volume oscillations of the endolymph in the scala media with subsequent mechanical deformation of Corti's organ, adducing as evidence the finding of an hydrops in certain of their animals, and the folding of Reissner's membrane following its collapse towards the basilar membrane. A careful study of the sixty deaf ears in the present series, especially of the younger animals, failed to produce any evidence either of cochlear or of saccular hydrops. It may be significant that a cochlear hydrops of slight to moderate degree was found in three coloured coat kittens with normal round window potentials and otherwise unremarkable cochlear histology.

Sagging of Reissner's membrane is the earliest light microscopical abnormality in the cochleo-saccular degeneration of the deaf Hedlund white mink (Sugiura & Hilding, 1970), but electron microscopy has revealed an earlier absence of mitochondria in the strial marginal cells (Hilding et al. 1967). A similar process of a sudden and rapid reduction in endolymph volume in the cochlear duct and saccule of the deaf white cat is already visible at day eight. A reduction of endolymph, but apparently not an over-production, is thus an early feature of the degenerative process in the cat, but whether the strial atrophy is causally involved in the degeneration of Corti's organ is at present uncertain. Investigations in other species have shown that these two processes may occur independently. Grüneberg (1955) presented evidence which contradicted his own, earlier hypothesis that the organ of Corti degeneration in the mouse was secondary to strial changes. In the mouse mutant piebald-lethal, long stretches of histologically and functionally normal hair cells occur in the presence of obvious abnormality of the entire length of the stria (Deol, 1967). On the other hand complete degeneration of Corti's organ occurs in the presence of only scattered patches of very moderate strial atrophy in the waltzing guinea pig (Ernstson, 1971). The strial degeneration in the cat may therefore be a concomitant manifestation of an as yet unidentified developmental defect.

The vessel of the basilar membrane has been shown to be of prime importance for the nutrition of the hair cells (Lawrence 1966). Electron microscopy in shaker 1 mice has revealed involution and obliteration of this vessel (Kikuchi & Hilding, 1967). Absence has also been described in the deaf dalmatian dog (Anderson et al. 1968), although Igarashi et al. (1972) found this vessel to be patent in deaf dalmatian puppies. Although some degree of involution is normal in the adult cat it would appear that patency of the lumen is retained in the deaf adult animal.

It is possible that the external sulcus cells are involved in the nutrition of Corti's organ (Crowe et al., 1934). The marked hyperplasia of these cells in the deaf cat has been described previously (Bosher & Hallpike, 1965) but this development occurs after the first signs of degeneration in the organ of Corti. An explanation for this apparent over-activity is not at present possible.

Retraction of the tectorial membrane into the inner spiral sulcus with formation of a globular mass and encasement in a layer of flattened cells has been described in hereditary (Fisch, 1959) and acquired human deafness (Lindsay & Hemenway 1954) and in the hereditary deafness of animals (Suga & Hattler 1970), and is very similar to the process found in the saccular otolithic membrane of the deaf white cat (Mair II). No other reports of the peculiar sphere-like structures present in the tectorial membrane could be found in the literature. These spheres first make their appearance along the undersur-

urements are largely in agreement with those of Retzius (1884)

Several investigators have confirmed the absence of round window potentials in the deaf white cat but the literature contains few descriptions of the early stages of the degenerative process in the cochlea. The only other detailed investigation reported that no morphological abnormalities were present in the first four days of life that the important stages were well advanced by the twelth day and virtually complete by the twenty first (Bosher & Hallpike 1965) The longest survival time in that series was 281 days These authors apparently observed simultaneous degeneration in all coils and concluded that the process was a degeneration of a morphologically mature organ in the first coil but in the apical coil was a combination of degeneration and arrested development More recently Bergsma & Brown (1971) reported that the organ of Corti in the deaf white cat may be normal in some areas whilst affected in others, but their study was restricted to *young* animals

The present material conclusively demonstrates *that the early stages of the degenerative process* in the cochlea of the deaf white cat follow *a regular pattern which parallels the postnatal* maturation of the hearing cochlea, with sequential *changes which spread longitudinally along* the duct from the upper half of the basal coil It would appear that the different coils of the cochlear duct must first reach a certain stage of morphological maturation before the genetically determined degeneration process can commence (Anderson et al. 1968)

In addition to the longitudinal progression along the duct there is also a radial progression across the basilar membrane, the outer hair cells being affected before the inner and the outermost row of the former before the two inner rows. Hair cell degeneration occurs first in the third row of the outer hair cells in the upper basal coil whilst the inner hair cells at both extremities of the cochlear duct have the longest survival time A similar finding of a radial progression across the duct has been reported in the waltzing guinea pig (Ernstson, 1971) the Hedlund white mink (Sugiura & Hilding, 1970) and in the dalmatian dog (Johnsson & Hawkins, 1972) The latter authors reported that the external hair cells first showed signs of degeneration in the second week after birth whilst degeneration of the inner hair cells did not commence until some weeks later The degenerative process in the deaf dalmatian dog and the white cat is therefore strikingly similar

Once the process of degeneration commences around the beginning of the second week it progresses rapidly and all structures in the basal coil are severely affected by the end of week three The process is however not virtually complete by the twenty-first day as maintained by Bosher & Hallpike (1965) but is progressive throughout the animal s life span Inner hair cell loss, for example, is minimal prior to the six to ten month stage and an eight year old animal shows a much greater degree of end-organ degeneration than does a two year old adult Moreover degeneration of the spiral ganglion with neuronal loss is not evident until towards the end of the first year (Mair IV). A similar process of progressive *degeneration with increasing age has been earlier* described in the saccule of the deaf white cat *(Mair II) The hereditary cohleo-saccular de*generation in the white cat is an all-or-none *phenomenon and once the process commences* it will progress in a fixed and constant pattern from the zones of predilection to involve all the *sensory and supporting cells of the cochlea and* the saccule

The upper basal coil is also the most severely affected in the similar cochleo-saccular degeneration found in several species of dog, and Igarashi et al (1972) concluded that this area may be the most fragile part of the cochlear end organ although the reason for this was unknown A radioautographic study of the inner ear development of the mouse has shown that the oldest cells of Corti s organ are found at the apex and *the youngest in the basal* coil (Ruben 1967) It is widely accepted that the phylogenetically younger pars inferior of the labyrinth is more susceptible to a variety of nocuous agents than is the older pars superior *The earlier appearance*

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face of the membrane in the twelve day deaf animal and are thereafter a constant feature of all pathological cochleae The spheres could be traced along the vestibular lip to the area of the interdental cells, but despite intensive search no direct evidence of secretion of these structures by the latter could be found

Autoradiographic studies have shown that the interdental cells secrete mucopolysaccharides, and several investigators have provided evidence that the interdental cells secrete a material into the tectorial membrane (Iurato 1962 Ishiyama et al 1970) It is therefore possible that the spheres consist of a material which would normally be incorporated into the substance of the tectorial membrane. The abnormal accumulation of this material first noted at day twelve may indicate that metabolic processes in the tectorial membrane have already ceased prior to this stage whereas the increase in size and numbers of the spheres with age may be due to a continued metabolic activity of the interdental cells.

The pattern of degeneration is in several respects, very similar in the cochlea and the saccule. In bilateral cases the histopathological findings are strikingly symmetrical In both the cochlea and the saccule there is a zone of predilection where the degeneration process commences, and which remains the most severely affected area Volume reduction of both structures commences simultaneously and is almost complete by day twelve Hair cell loss is first evident around the fourth week and the last surviving hair cells are found at the end of the second year in those areas of the saccule and cochlea which are furthest removed from the sites of predilection. In contrast the afferent nerves present markedly different findings Neuronal loss does not occur in the saccular division of Scarpa's ganglion (Mair II) whereas a progressive age-related ganglion cell loss is found in the spiral ganglion of the cochlea (Mair IV)

In human acquired cochleo-saccular degeneration Reissner's membrane has either been normally situated or only slightly depressed (Schuknecht et al 1965 Hemenway et al 1969) The obliteration of the cochlear duct and of the greater part of the saccular lumen at an early stage in the deaf white cat may have differential diagnostic significance for congenital deafness of the Scheibe type in humans. An additional important feature is the orderly and systematic progression which characterises this type of hereditary degeneration. Conclusions from this series will however remain purely speculative, and emphasises once again the need for further studies of human material

ZUSAMMENFASSUNG

Es wurde der Ablauf der Degeneration in der Cochlea bei der erblich tauben weissen Katze in verschiedenen Altersklassen untersucht. Die frühen Degenerationsstadien wurden mit den Stadien der postnatalen morphologischen Reifung beim hörenden Tier verglichen. Beide Prozesse beginnen in der oberen Hälfte der basalen Windung und schreiten longitudinal entlang des Ductus fort.

Die Obliteration des Cochleaganges und die Degeneration der Stria vascularis und die herausragenden frühen Geschehen es wurde jedoch kein Hydrops beobachtet.

Es kommt auch zu einer radialen Ausbreitung durch die Basilarmembran hindurch die äusseren Haarzellen degenerieren früher als die inneren. Bemerkenswert jedoch erst beim 12 Tage alten tauben Tier nachweisbar ist das Auftreten kleiner homogener Kügelchen in der Membrana tectoria, diese Strukturen scheinen aus dem Bereich der interdentalen Zellen zu stammen.

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extent of spiral ganglion degeneration found in different temporal bones (Brown & Chung, 1971).

The present report contains the results of a quantitative study of the degeneration process in the spiral ganglion of the hereditarily deaf white cat.

MATERIAL AND METHODS

A white cat stock of 96 animals was accumulated over a period of time. Recordings of cochlear potentials from round window electrodes showed that 26 white coat animals were bilaterally and 8 unilaterally deaf. Both the hearing and the deaf animals were sacrificed at varying ages from the early postnatal period up to eight years of age by the standard method of intravital cardiac perfusion using Heidenhain's Susa solution as fixative. The temporal bones were processed for light microscopy and embedded in celloidin with the mid-modiolar axis of the cochlea orientated in the horizontal plane. Serial sections were cut at a thickness of 20 microns and every tenth, and in some cases every fifth, section stained with haematoxylin and eosin.

The development of the degeneration process was first studied in the end-organ, and the time course established for the principal constituents of the cochlear duct (Mair). The degeneration of the spiral ganglion was investigated and compared with the age of the animal and the degree of end-organ degeneration.

Graphic reconstructions of the organ of Corti and the spiral ganglion were performed in fourteen ears according to the technique of Guild (1921). The spiral ganglion was subdivided into six segments by the vertical line through the tangential sections as shown in Fig. 13. The lengths of the reconstructed spiral ganglions and the six segments were measured, corrected for magnification, and the mean lengths and standard deviations calculated.

Spiral ganglion cell counts were performed in seventeen functionally and histologically normal ears of different age groups, and in forty-eight of the deaf ears. Counts of the remaining twelve deaf ears were not performed due to a variety

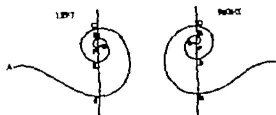


Fig. 13. Diagram of reconstructed spiral ganglion. The spiral ganglion, AO, is subdivided into six segments by the vertical line which joins the tangentially cut sections at B, C, D, E and F.

of technical imperfections in the histological processing. Ganglion cells were counted under high-dry magnification using an eyepiece-reticule, every tenth, and in some ears every fifth, section being studied. All ganglion cells which contained a definite nucleolus were counted, the focus being constantly varied from upper to lower surface of the sections. As every tenth section was counted a multiplication factor of 9.5 was used to calculate the total ganglion cell populations and simultaneously correct for the possibility of split nucleoli (Schuknecht, 1960). In those ears in which every fifth section was counted the average of the two measurements was taken and then multiplied by the same factor. In each ear the number of ganglion cells at the different levels of the cochlea were transferred to the appropriate points in the standard reconstruction graph described above, and the neuron densities per millimetre of the six subdivisions of the spiral ganglion calculated.

RESULTS

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The present report contains the results of a quantitative study of the degeneration process in the spiral ganglion of the hereditarily deaf white cat.

MATERIAL AND METHODS

A white cat stock of 96 animals was accumulated over a period of time. Recordings of cochlear potentials from round window electrodes showed that 26 white coat animals were bilaterally and 8 unilaterally deaf. Both the hearing and the deaf animals were sacrificed at varying ages from the early postnatal period up to eight years of age by the standard method of intravital cardiac perfusion using Heidenhain's Susa solution as fixative. The temporal bones were processed for light microscopy and embedded in celloidin with the mid-modiolar axis of the cochlea orientated in the horizontal plane. Serial sections were cut at a thickness of 20 microns and every tenth, and in some cases every fifth, section stained with haematoxylin and eosin.

The development of the degeneration process was first studied in the end-organ, and the time course established for the principal constituents of the cochlear duct (Mair). The degeneration of the spiral ganglion was investigated and compared with the age of the animal and the degree of end-organ degeneration.

Graphic reconstructions of the organ of Corti and the spiral ganglion were performed in fourteen ears according to the technique of Guild (1921). The spiral ganglion was subdivided into six segments by the vertical line through the tangential sections as shown in Fig. 13. The lengths of the reconstructed spiral ganglions and the six segments were measured, corrected for magnification, and the mean lengths and standard deviations calculated.

Spiral ganglion cell counts were performed in seventeen functionally and histologically normal ears of different age groups, and in forty-eight of the deaf ears. Counts of the remaining twelve deaf ears were not performed due to a variety

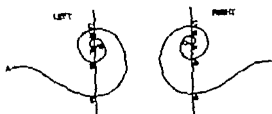


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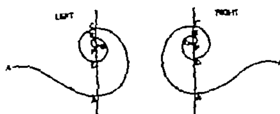


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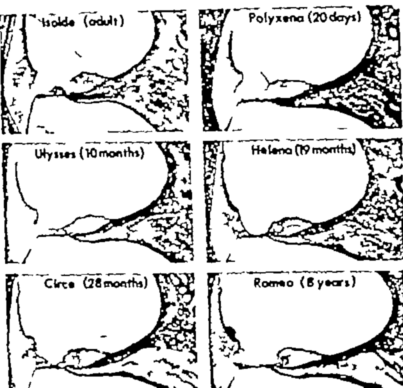


Fig. 15. Upper half of coil one showing the cochlear duct and Rosenthal's canal. Isolde, normal appearance of adult, hearing animal. Polyxena, 20 day deaf cat showing commencing degeneration of cochlear duct and normal density of ganglion cells. Ulysses, 10 month, deaf animal with marked end-organ degeneration and numerous ganglion cells in Rosenthal's canal. Helena, 19 month, deaf animal showing definite reduction in ganglion cell population. Greater degrees of ganglion cell loss are shown in the 28 month young adult (Circe) and in the 8 year adult (Romeo) animals.

ganglion cells show definite evidence of chromatolysis, whereas the majority of cells are indistinguishable from those of the hearing adult (Fig. 17 Isolde). A significant number of degenerating neurons first appears after the ten month stage. At nineteen months (Fig. 17 Helena) the majority of the surviving neurons have an unremarkable light microscopical appearance, but some degenerating ganglion cells are readily found. In the adult, many of the surviving neurons appear to be degenerating. The cells are considerably larger, have an eccentric deeply-staining, irregular nucleus, the cytoplasm is more homogeneous, occasionally vacuolar, and Nissl granules are no longer evident (Fig. 17 Circe & Romeo).

Statistical confirmation for the theory of increasing neuronal degeneration as a function of age in the deaf animals was obtained by spiral ganglion reconstructions and ganglion cell counts. The lengths of the entire ganglion and the six subdivisions from fourteen reconstructed ears are presented in Table 13. The mean length of the spiral ganglion was 10.67 mm. In Table 14 are shown the total neuron counts and the neuron densities per mm of the six subdivisions of Rosenthal's canal in seventeen histologically and electrophysiologically normal ears. The mean total neuron count was found to be 51 770, with a range from 45 020 to 57 541. The total neuron counts in adult hearing cats are not significantly different from those found in young hearing animals, and the presence of degeneration in the contralateral ear has likewise no discernible influence in this series. The neuron densities per mm of the spiral ganglion are very

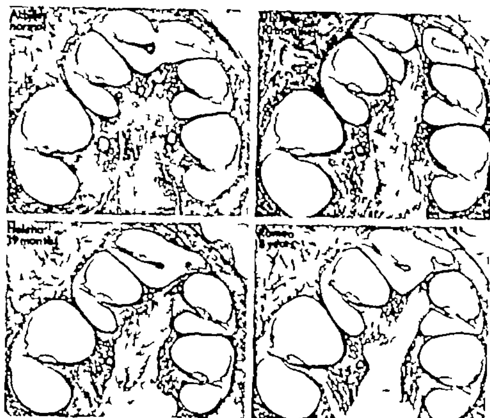


Fig 14 Approximately mid-modiolar sections of the right cochlea. Achilles adult, hearing animal showing normal appearance of cochlear duct, spiral ganglion and cochlear nerve. Ulysses. 10 month, deaf animal with degeneration of the cochlear duct. The cochlear nerve and spiral ganglion appear unremarkable. Helena 19 month, deaf animal with marked scala media degeneration and obvious ganglion cell loss in coils one and two and definite degeneration of the cochlear nerve. Romeo 8 year deaf animal with almost complete disappearance of cochlear nerve fibres and only a few ganglion cells in each coil

practically devoid of ganglion cells in the former and the cochlear nerve almost totally degenerated Progressively lesser degrees of ganglion cell loss and nerve degeneration are seen in the nineteen month (Fig. 14 Helena) and the ten month (Fig. 14 Ulysses) deaf ears. Indeed in the latter the appearance of the ganglion is little different from that found in the hearing adult (Fig. 14 Achilles) although the degeneration of the end organ is already well advanced at that age

The cochlear duct and the corresponding segment of the spiral ganglion from the upper half of the basal coil of six animals are shown in higher magnification in Fig. 15 The appearance of the end-organ in the hearing adult (Fig. 15 Isolde) is in sharp contrast to that found in all the deaf ears This picture of cochlear duct degeneration is already well advanced by day twenty (Fig 15 Polyxena) and is thereafter progressive with age. The spiral ganglion in the ten month deaf ear (Fig. 15 Ulysses) is very similar to that of the hearing adult (Fig. 15 Isolde) and it is first at the nineteen month stage (Fig. 15 Helena) that a reduction in number of neurons becomes readily apparent The density of the spiral ganglion cell population in Rosenthal's canal decreases progressively with age (Fig 15 Circe & Romeo) In Fig 16 are shown higher power views of the spiral ganglions already presented in the previous illustration The progressive ganglion cell loss and degeneration of the afferent nerve fibres with age are immediately apparent.

In Fig 17 are shown high power views of the areas marked by arrows in the previous figure The spiral ganglion cells of the hearing adult (Fig 17 Isolde) have a characteristic appearance with well differentiated Nissl substance. In the twenty day (Fig 17 Polyxena) and the ten month (Fig 17 Ulysses) deaf animals some of the

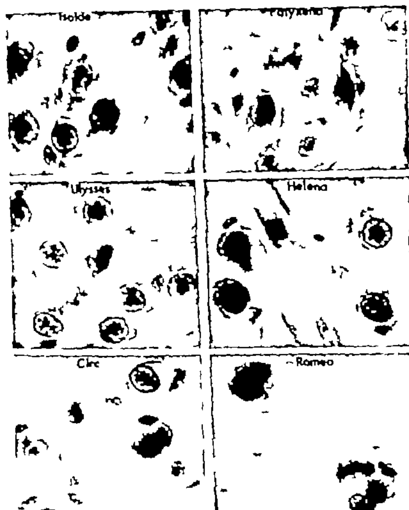


Fig. 17. Higher power views of ganglion cells marked by arrows in Fig. 16. Normal appearance of spiral ganglion cells in the hearing adult cat (Isolde). Chromatolysis is evident in some of the ganglion cells in the 20 day (Polyxena) and 10 month (Ulysses) deaf ears, while others contain Nissl granules and have normal appearing nuclei. In the 19 month (Helena), 28 month (Circe) and 8 year (Romeo) deaf ears are found scattered ganglion cells which are larger, with homogeneous, occasionally vacuolar cytoplasm and densely staining nuclei.

subsequent compression of the ganglion cells. All three ears at the ten month stage have total neuron counts at the lower limit of the range of normal. In all deaf ears from cats over the age of ten months there is a significant reduction in total neuron count, and this correlates approximately with the age of the animal. The total neuron counts of the functional and pathological ears are presented graphically in Fig. 18.

Table 15 also demonstrates that ganglion cell loss occurs first in the central portion of the spiral ganglion, segments BC, CD and DE, and this area is consistently the most severely affected. The greatest absolute and relative degree of ganglion cell loss is found in segment CD, i.e. the upper half of the basal coil, in the two oldest animals in the series (Alpha & Romeo).

DISCUSSION

Estimations of the total number of neurons in the spiral ganglion of the cat have varied con-

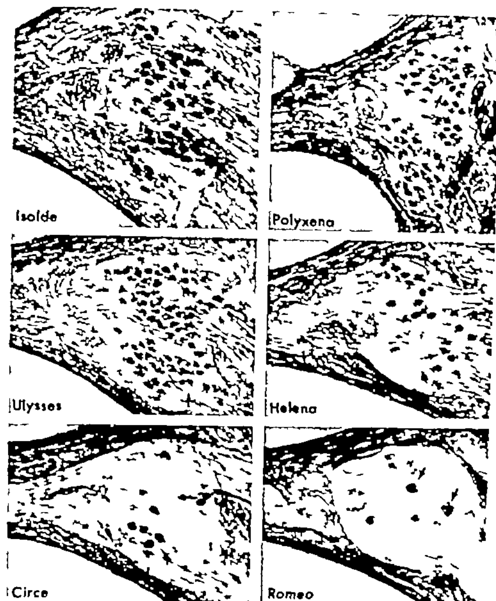


Fig 16 Higher power views of spiral ganglions from the preceding figure. Ganglion cell densities are approximately similar in the hearing adult (Isolde), the 20 day deaf (Polyxena) and the 10 month deaf (Ulysses) ears, whereas progressive ganglion cell loss with increasing connective tissue replacement are found in the 19 month (Helena), 28 month (Circe) and 8 year (Romeo) deaf animals. Arrows mark areas shown in succeeding figure.

similar in the central segments BC, CD and DE. At both extremities, segments AB and FG the mean densities are higher and there is a significantly greater range of variation

The total neuron counts and the neuron densities of forty-eight pathological ears are shown in Table 15 The data are presented in ascending age groups up to and including the ten month stage and are thereafter arranged in ascending order of ganglion cell loss. This is found to correspond closely with the age of the animal It should be noted that the exact ages of the adult (over two years) deaf animals were unfortunately not known but the oldest, Romeo was at least two years older than the rest of the series. Up to and including the six month deaf animal the total neuron counts are almost entirely within the range of normal presented in Table 14 In only one instance Ino is the total count of 44 355 slightly below the lower limit of 45 020 found in the series of normals Ganglion cell counts in young animals are difficult and more liable to inaccuracies due to the plentiful vascularisation in the modiolus at this stage with

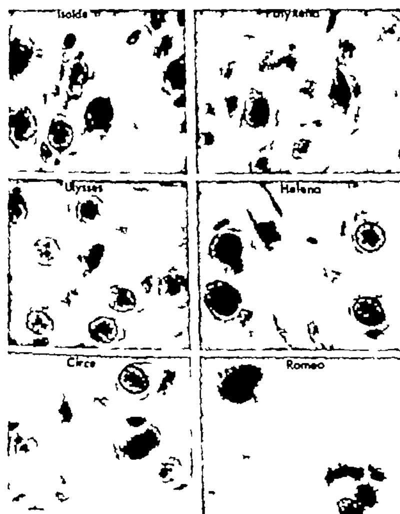


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Table 13 *Lengths in millimetres of spiral ganglion and ganglion segments Reconstructions of fourteen ears*

Lt = left ear Rt = right ear m = months, Ad = adult hg = hearing df = deaf

Animal	Side	Age	Status	Segments AB	BC	CD	DE	EF	FG	Total AG
Aphrodite	Lt	1 m	df	1 92	4 20	2.38	1.58	1.04	0 46	11.58
Aphrodite	Rt	1 m	df	1 76	4.04	2.20	1 78	1 06	0 40	11.4
Aerope	Lt	Ad	hg	1 64	4 08	2.12	1 42	0 66	0.34	10 26
Aerope	Rt	Ad	df	1 70	4 16	2.36	1.5	0 74	0	10.70
Cassandra	Lt	10 m	df	2 06	4 14	2.14	1.38	0 92	0 18	10 82
Cassandra	Rt	10 m	hg	1 68	3 96	2.06	1.30	0 80	0.32	10 1
Helena	Lt	19 m	hg	1 84	4.54	1 94	1.36	0 78	0.24	10.70
Helena	Rt	19 m	df	1 78	4.3	2.3	1.58	0.7	0.16	10 88
Princess	Lt	Ad	df	1 7	3 98	2.04	1 60	0.96	0.26	10 56
Princess	Rt	Ad	df	1 60	4.26	1.84	1 66	0 8	0.28	10 46
Romeo	Lt	Ad	df	1 90	4 10	.00	1 42	0 72	0.44	10 58
Romeo	Rt	Ad	df	1 90	3 90	1.86	1.48	0.70	0 42	10 6
Tau	Lt	Ad	df	1.44	4 06	2.01	1 74	0 88	0.50	10.66
Tau	Rt	Ad	hg	1 48	4 1	1.96	1 70	0.9	0 44	10 6
Mean				1 74	4 13	2.09	1.54	0 84	0 33	10 67
S D				0.173	0.163	0.174	0 150	0.128	0 112	0.385

Table 14 *Spiral ganglion cell counts in seventeen functionally and histologically normal ears Total numbers of neurons and neuron densities per millimetre of the six spiral ganglion segments*

Lt = left ear Rt = right ear d = days, m = months, Ad = adult

Animal	Side	Age	Neuron densities/mm AB	BC	CD	DE	EF	FG	Total
Maia	Lt	6 d	5 350	4 624	4 500	4 077	5 541	9 3	51 784
Maia	Rt	6 d	5 033	4 076	4 136	4 151	3 8 3	7 081	46 180
Kit 24	Rt	1 d	5 934	4 970	4 900	4 948	5 643	5 815	55 375*
Polyxena	Rt	0 d	6 781	4 504	4 773	4 68	5 633	3 657	5 885
Beta	Rt	6 d	5 4 7	3 80	3 627	3 331	5 949	6 564	45 020*
Kit 20	Rt	7 d	6 322	5 035	4 781	4 997	5 813	7 053	56 696*
Cassandra	Rt	10 m	5 394	4 790	4 718	4 651	5 790	5 843	50 970*
Helena	Lt	19 m	6 614	4 662	4 711	5 095	6 011	5 786	55 408*
Aerope	Lt	Ad	5 228	4 810	5 168	4 8 7	6 543	6 95	54 967*
Aethra	Rt	Ad	5 53	4 667	5 059	4 743	5 281	6 851	53 000
Alpha	Lt	Ad	5 471	4 575	5 83	6 705	5 11	9 356	57 541
Endymion	Rt	Ad	6 797	4 318	4 048	3 806	5 089	5 469	45 837
Greta	Rt	Ad	5 968	4 704	4 450	4 503	3 959	5 843	51 300
Isolde	Rt	Ad	4 357	3 949	4 673	4 577	4 863	4 146	46 160
Judy	Lt	Ad	7 644	4 501	5 045	4 959	5 59	6 391	56 601
Mercury	Rt	Ad	3 975	4 768	5 096	5 354	5 723	6 103	50 036
Tau	Rt	Ad	5 11	4 379	4 068	5 083	5 558	6 765	50 383
Mean			5 691	4 508	4 68	4 651	5 387	6 41	51 770
S D			9 6 3	340 3	520.5	653 4	690 6	1 45 7	4 101 9

Contralateral ear deaf
* Colour coat animal
Every fifth section counted

Table 15 *Spiral ganglion cell counts in forty-eight deaf ears Total numbers of neurons and neuron densities per millimetre of the six spiral ganglion segments*

Lt left ear Rt right ear d = days, m = months, Ad = adult

Animal	Side	Age	Neuron densities/mm						Total
			AB	BC	CD	DE	EF	FG	
Medea	Lt	10 d	6 700	4 373	4 369	4 454	5 010	5 239	52 582
Astyanax	Lt	12 d	5 100	4 226	4 737	3 553	4 264	5 124	46 873
Astyanax	Rt	12 d	5 435	4 368	4 750	3 449	4 654	3 800	47 898[a]
Polyxena	Lt	20 d	5 708	4 335	3 786	3 867	5 440	3 352	47 314[a]
Beta	Lt	26 d	7 109	4 090	3 454	3 313	4 773	3 800	46 844
Ino	Lt	43 d	6 767	3 687	3 204	3 756	4 116	4 318	44 355
Ino	Rt	43 d	5 599	4 157	3 795	3 914	4 518	4 275	46 079
Pelias	Lt	47 d	5 744	4 124	3 536	3 942	5 044	3 685	45 951
Pelias	Rt	47 d	4 985	4 402	4 455	4 016	5 146	4 376	48 117
Hermes	Rt	53 d	6 672	4 189	3 535	3 313	4 671	6 016	47 348
Cleo	Lt	57 d	5 105	4 421	4 500	4 571	5 441	5 499	50 055
Cleo	Rt	57 d	6 016	4 577	3 930	4 497	4 796	5 758	50 480
Hector	Lt	6 m	6 181	4 483	3 877	4 478	6 424	7 801	52 240
Hector	Rt	6 m	7 010	4 619	3 991	4 399	6 231	8 663	54 482
Cassandra	Lt	10 m	6 672	3 981	3 072	3 491	6 375	5 239	46 768[a]
Ulysses	Rt	10 m	4 859	3 632	4 019	4 466	5 372	8 204	45 951
Ulysses	Lt	10 m	4 587	3 915	4 335	3 812	3 867	7 139	44 726
Hercules	Lt	Ad	6 379	2 627	2 114	2 677	3 766	6 996	35 786
Orpheus	Rt	14 m	6 726	3 110	2 486	1 092	2 364	5 211	35 131
Caruso	Lt	16 m	6 088	3 182	2 104	1 777	2 963	2 389	34 143
Aphrodite	Lt	21 m	5 594	2 530	2 413	2 733	3 461	3 599	33 530[a]
Aphrodite	Rt	21 m	5 225	2 511	1 975	2 381	4 038	4 131	32 010[a]
Hercules	Rt	Ad	5 116	2 627	1 332	1 734	4 [illegible]91	5 124	30 751
Caruso	Rt	16 m	4 874	2 609	2 032	1 129	2 002	1 958	27 748
Adam	Rt	21 m	5 465	1 928	1 704	1 792	2 990	1 842	27 141
Thisbe	Rt	Ad	6 557	1 647	790	1 246	2 884	5 786	26 115
Adam	Lt	21 m	3 740	2 185	1 931	2 098	2 986	950	25 621
Helena	Rt	19 m	4 570	2 289	1 354	1 045	2 550	3 943	25 289[a, b]
Venus	Rt	Ad	3 353	1 767	2 041	2 587	3 223	3 080	25 118
Acrope	Rt	Ad	3 863	2 187	1 515	1 203	1 829	4 309	23 812
Venus	Lt	Ad	3 019	1 743	1 995	2 048	703	3 023	23 047
Persephone	Lt	Ad	3 450	1 902	1 004	1 437	3 371	5 527	22 914
Thisbe	Lt	Ad	4 112	1 532	818	1 234	3 574	6 588	22 268
Tea	Lt	Ad	4 160	1 568	713	873	1 420	5 196	19 498[a]
Circe	Lt	Ad	3 653	1 541	904	1 012	1 889	3 653	18 848
Persephone	Rt	Ad	2 621	1 486	818	1 079	3 121	5 527	18 515
Eva	Lt	22 m	3 663	1 500	482	485	1 776	2 620	17 404
Eva	Rt	22 m	3 178	1 390	578	666	1 967	2 303	15 751
Circe	Rt	Ad	2 206	1 127	723	846	1 764	1 727	13 357
Princess	Lt	Ad	2 812	683	393	34[illegible]	1 665	950	11 105
Psyche	Lt	Ad	2 795	579	250	296	1 255	4 347	10 611
Princess	Rt	Ad	2 381	646	300	34[illegible]	973	4 231	10 488
Psyche	Rt	Ad	2 588	380	245	395	1 017	4 635	10 402
Agamemnon	Rt	Ad	1 987	310	500	380	2 047	3 311	10 193
Agamemnon	Lt	Ad	1 862	536	350	438	2 228	3 908	9 880
Alpha	Rt	Ad	759	124	77	339	634	3 281	4 132[a]
Romeo	Rt	Ad	909	197	75	120	288	3 079	3 234
Romeo	Lt	Ad	829	178	77	143	276	1 381	3 220[b]

[a] Contralateral ear normal
[b] Every fifth section counted

siderably In studies based on ganglion cell counts, Howe (1935) found a range of normal of 44 798 to 57 494 with a mean value of 49 962 for a series of nine ears, whilst Schuknecht (1960) reported the much lower figure of 39 000 Analysis of the myelinated fibres in the cochlear nerves of six cats produced an average of 51 755 (Gacek & Rasmussen, 1961), which is remark

Table 13 *Lengths in millimetres of spiral ganglion and ganglion segments Reconstructions of fourteen ears*

Lt – left ear Rt – right ear m – months, Ad – adult hg – hearing df – deaf

Animal	Side	Age	Status	Segments AB	BC	CD	DE	EF	FG	Total AG
Aphrodite	Lt	21 m	df	1 92	4.20	2.38	1.58	1 04	0 46	11.58
Aphrodite	Rt	21 m	df	1 76	4.04	2.20	1 78	1 06	0 40	11.[illegible]4
Aerope	Lt	Ad	hg	1 64	4 08	[illegible]12	1 42	0 66	0.34	10.26
Aerope	Rt	Ad	df	1 70	4 16	2.36	1.5	0.74	0.22	10 70
Cassandra	Lt	10 m	df	2.06	4 14	[illegible]14	1.38	0 9[illegible]	0.18	10.82
Cassandra	Rt	10 m	hg	1 68	3.96	[illegible]06	1.30	0 80	0.3	10 12
Helena	Lt	19 m	hg	1.84	4.54	1 94	1.36	0 78	0 [illegible]4	10.70
Helena	Rt	19 m	df	1 78	4.32	2.32	1.58	0.72	0.16	10 88
Princess	Lt	Ad	df	1 72	3 98	2.04	1 60	0 96	0.[illegible]6	10.56
Princess	Rt	Ad	df	1 60	4.26	1.84	1 66	0 82	0 28	10 46
Romeo	Lt	Ad	df	1.90	4 10	[illegible]00	1 4[illegible]	0 72	0.44	10.58
Romeo	Rt	Ad	df	1 90	3 90	1.86	1 48	0.70	0 4	10.26
Tau	Lt	Ad	df	1 44	4 06	2 04	1 74	0.88	0.50	10 66
Tau	Rt	Ad	hg	1 48	4 12	1.96	1 70	0 92	0.44	10 62
Mean				1 74	4 13	2.09	1.54	0 84	0 33	10 67
S D				0 173	0.16[illegible]	0 174	0 150	0.128	0 112	0.385

Table 14 *Spiral ganglion cell counts in seventeen functionally and histologically normal ears Total numbers of neurons and neuron densities per millimetre of the six spiral ganglion segments*

Lt – left ear Rt – right ear d – days, m – months, Ad – adult

Animal	Side	Age	Neuron densities/mm AB	BC	CD	DE	EF	FG	Total
Mala	Lt	6 d	5 350	4 624	4 500	4 077	5 541	9 3[illegible]7	51 784
Mala	Rt	6 d	5 033	4 076	4 136	4 151	3 823	7 081	46 180
Kit 24	Rt	12 d	5 934	4 970	4 900	4 948	5 643	5 815	55 375[b]
Polyxena	Rt	20 d	6 781	4 504	4 773	4 268	5 633	3 657	52 885[a]
Beta	Rt	26 d	5 427	3 802	3 627	3 331	5 949	6 564	4[illegible] 020[a]
Kit 20	Rt	27 d	6 3[illegible]2	5 035	4 781	4 997	5 813	7 053	56 696[b]
Cassandra	Rt	10 m	5 394	4 290	4 718	4 651	5 790	5 843	50 920[a]
Helena	Lt	19 m	6 614	4 662	4 711	5 095	6 011	5 786	55 408
Aerope	Lt	Ad	5 228	4 810	5 168	4 8[illegible]7	6 543	6 952	54 967[a]
Aethra	Rt	Ad	5 253	4 667	5 059	4 743	5 281	6 851	53 000
Alpha	Lt	Ad	5 471	4 575	5 832	6 205	[illegible] 112	9 356	57 541
Endymion	Rt	Ad	6 797	4 318	4 058	3 806	5 089	5 469	45 837
Greta	Rt	Ad	5 968	4 704	4 450	4 503	3 959	5 843	51 [illegible]00
Isolde	Rt	Ad	4 357	3 949	4 673	4 577	4 863	4 146	46 160
Judy	Lt	Ad	7 644	4 501	5 045	4 959	5 259	6 391	56 601
Mercury	Rt	Ad	[illegible] 975	4 768	5 096	5 354	5 723	6 103	50 036
Tau	Rt	Ad	[illegible] [illegible]11	4 379	4 068	5 083	5 558	6 765	50 383
Mean			[illegible] 691	4 908	4 68[illegible]	4 681	5 387	6 412	51 770
S D			9[illegible]6 3	340.3	520.5	653 4	690 6	1 452 7	4 103 9

Contralateral ear deaf
• Colour coat animal
Every fifth section counted

Table 15. *Spiral ganglion cell counts in forty-eight deaf ears. Total numbers of neurons and neuron densities per millimetre of the six spiral ganglion segments*

Lt left ear Rt right ear d = days, m = months, Ad = adult

Animal	Side	Age	Neuron densities/mm AB	BC	CD	DE	EF	FG	Total
Medea	Lt	10 d	6 700	4 373	4 569	4 454	5 010	5 239	52 582
Astyanax	Lt	12 d	5 100	4 226	4 737	3 553	4 264	5 124	46 873
Astyanax	Rt	12 d	5 435	4 368	4 750	3 449	4 654	3 800	47 898[a]
Polyxena	Lt	20 d	3 708	4 335	3 786	3 867	5 440	3 152	47 314
Beta	Lt	26 d	7 109	4 090	3 454	3 313	4 773	3 800	46 844[a]
Ino	Lt	43 d	6 787	3 687	3 204	3 756	4 116	4 318	44 355
Ino	Rt	43 d	5 599	4 157	3 795	3 914	4 518	4 275	46 079
Pelias	Lt	47 d	5 744	4 1[illegible]4	3 536	3 942	5 044	3 685	45 951
Pelias	Rt	47 d	4 985	4 402	4 455	4 016	5 146	4 376	48 117
Hermes	Rt	53 d	6 672	4 189	3 555	3 313	4 671	6 016	47 348
Clio	Lt	57 d	5 105	4 421	4 500	4 571	5 541	5 499	50 055
Clio	Rt	57 d	6 016	4 577	3 950	4 497	4 796	5 758	50 483
Hector	Lt	6 m	6 181	4 483	3 877	4 478	6 424	7 801	52 240
Hector	Rt	6 m	7 010	4 619	3 991	4 399	6 231	8 665	54 482
Cassandra	Lt	10 m	6 672	3 981	3 072	3 491	6 175	5 239	46 768[a]
Ulysses	Rt	10 m	4 859	3 632	4 019	4 466	5 372	8 204	45 951
Ulysses	Lt	10 m	4 587	3 915	4 355	3 812	3 867	7 139	44 726
Hercules	Lt	Ad	6 279	2 627	2 114	2 677	3 766	6 996	35 786
Orpheus	Rt	14 m	6 726	3 110	2 484	1 092	2 364	5 211	35 131
Orfeo	Lt	16 m	6 088	3 182	2 104	1 777	2 963	2 389	34 143
Aphrodite	Lt	21 m	5 594	2 530	2 413	2 733	3 461	3 599	33 530[a]
Aphrodite	Rt	21 m	5 225	2 511	1 975	2 381	4 038	4 131	32 010[a]
Hercules	Rt	Ad	5 116	2 627	1 332	1 734	4 591	5 124	30 751
Orfeo	Rt	16 m	4 874	2 609	2 032	1 129	2 002	1 958	27 740
Adam	Rt	21 m	5 465	1 928	1 704	1 79[illegible]	2 990	1 842	27 141
Thisbe	Rt	Ad	6 557	1 647	790	1 246	2 884	5 786	26 115
Adam	Lt	21 m	3 740	2 185	1 931	2 098	2 986	990	25 621
Helena	Rt	19 m	4 570	2 289	1 354	1 045	2 550	3 943	25 289[a] [b]
Venus	Rt	Ad	3 353	1 767	2 041	2 587	3 223	3 080	25 118
Aerope	Rt	Ad	3 863	2 187	1 515	1 203	1 929	4 304	23 811 [b]
Venus	Lt	Ad	3 019	1 743	1 995	2 048	2 703	3 023	23 047
Persephone	Lt	Ad	3 450	1 902	1 004	1 437	3 371	5 527	22 914
Thisbe	Lt	Ad	4 112	1 532	818	1 234	3 574	6 588	22 268
Tas	Lt	Ad	4 160	1 568	713	872	1 470	5 196	19 498[a] [b]
Circe	Lt	Ad	3 653	1 541	904	1 012	1 889	3 653	18 848
Persephone	Rt	Ad	2 621	1 486	818	1 079	3 121	5 527	18 515
Eva	Lt	22 m	3 663	1 500	682	685	1 776	2 620	17 404
Eva	Rt	22 m	3 178	1 390	578	666	1 967	303	15 751
Circe	Rt	Ad	2 206	1 127	723	846	1 764	1 727	13 357
Princess	Lt	Ad	2 812	683	395	542	1 685	990	11 105
Psyche	Lt	Ad	2 795	529	250	296	1 255	4 347	10 611
Princess	Rt	Ad	2 381	646	300	542	973	4 231	10 488
Psyche	Rt	Ad	2 588	580	245	395	1 017	4 635	10 402
Agamemnon	Rt	Ad	1 987	510	500	500	2 047	3 311	10 193
Agamemnon	Lt	Ad	1 86[illegible]	536	330	438	2 228	2 908	9 690
Alpha	Rt	Ad	799	1[illegible]4	77	339	634	3 281	4 132[a]
Romeo	Rt	Ad	909	192	75	120	288	1 079	3 234
Romeo	Lt	Ad	829	178	77	123	276	1 381	3 220[b]

[a] Contralateral ear normal
[b] Every fifth section counted

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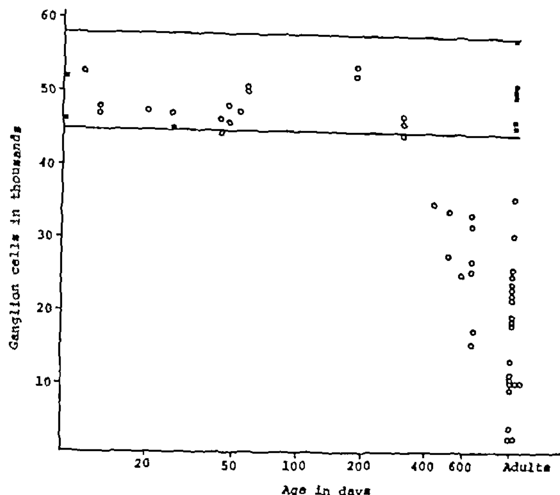


Fig 18 Total ganglion cell counts of seventeen hearing and forty-eight deaf ears. Age is represented logarithmically along the abscissa and ganglion cell counts in thousands along the ordinate. The range of normal for this series is shown by the two horizontal lines. ● = ganglion cell count in hearing ear O = ganglion cell count in deaf ear

ably similar to the figure of 51 770 from the present series of seventeen ears The slightly higher figure of 55 000 has been reported by Spoendlin (1972) on the basis of fibre counts in the osseous spiral lamina.

The mean length of the spiral ganglion in this material, 10 67 mm, is close to the figure of 11 2 mm reported by Schuknecht (1960) A higher neuron density in the central portion of the human spiral ganglion was found by Guild (1932) and in the cat by Spoendlin (1972) whereas Schuknecht (1960) reported that the neuron population densities in the latter species were uniform throughout the length of the spiral ganglion The present material supports the latter finding, but demonstrates a slightly greater density at both extremities of Rosenthal s canal This may represent compensation for the greater length of the cochlear duct and the unequal representation of the latter along the shorter spiral ganglion (Sando 1965) The greater variability in neuron densities found in the hook region and at the apex are probably a result of the investigational technique and counting based on studies of consecutive sections instead of every tenth or fifth would almost certainly reveal a greater uniformity

The degeneration pattern of the structures in the cochlear duct of the deaf white cat has been previously shown to be closely related to the age of the animal (Mair III) Degeneration commences at the end of the first postnatal week progresses rapidly in the subsequent two to three weeks, and thereafter more slowly through

out the animal's life span. In the six month deaf cat the organ of Corti shows an advanced degree of degeneration of all cell types, but the nerve fibres in the osseous spiral lamina reveal no abnormalities on light microscopy and the ganglion cell count is within the range of normal. By ten months, the neuron counts of the three ears in this series are at, or slightly below the lower limit of the range of normal, but in the next age group represented, fourteen months, the ganglion cell count is already reduced by approximately 30%. Increasingly older animals show a successively greater reduction in total ganglion cell numbers, and by eight years (Romeo) only 6% of the neurons remain. The two ears of bilaterally deaf animals show an approximately symmetrical degeneration pattern, the differences in ganglion cell counts which occur being well within the range of variability found in the hearing animals. This bilateral symmetry is not surprising in view of the symmetrical end-organ degeneration found in the cochlea (Mair III).

A similar pattern of a primary end-organ degeneration and a delayed degeneration of the afferent cochlear neurons has been reported in several mouse mutants (Grüneberg, 1955 Deol, 1970) and in the waltzing guinea pig (Ernstson, 1971). Statistical evidence in the form of ganglion cell counts correlated with age is, however lacking in the literature. Only in three mouse mutants have quantitative studies in the form of ganglion cell densities per unit area of the spiral ganglion been made (Deol, 1954). The latter author demonstrated a progressive ganglion cell loss, which continued throughout life although the rate of degeneration was less in the older animals. In one species of mouse, varitint-waddler the spiral ganglion degeneration was found to occur prior to changes in Corti's organ, but it is possible that electron microscopy would clarify this apparent exception.

Normal cochlear neurons have been reported in the deaf dalmatian dog (Bredberg, 1968), and in only one of the animals studied by Anderson et al. (1968) was a reduction of spiral ganglion cells found. Schuknecht et al. (1965) also found a normal neuron density in the deaf dalmatian dog and considered that the degenerative changes in the cochlear duct must have occurred during embryological development, adducing as evidence the rapid secondary neuronal degeneration which occurs subsequent to acquired, postnatal lesions of the end-organ (Schuknecht, 1953). By implication, the cochleo-saccular degeneration in the deaf dalmatian dog would therefore be classified in Grüneberg's (1955) morphogenetic group. Comparison with the morphologically similar cochleo-saccular degeneration in the white cat would tend to refute this suggestion, as it is clearly demonstrated in the present material that neuronal and end-organ degeneration are separated by a considerable interval of time. That such a comparison is valid is shown by the earlier report of spiral ganglion cell degeneration in all deaf dalmatian dogs studied by Lurie (1948). There is probably considerable inter-species variation in the time-course of hereditary cochleo-saccular degeneration, normality of the spiral ganglion having been reported until late in adult life in human material (Gacek, 1971).

Both the postnatal maturation of the normal cat cochlea and the process of cochlear end-organ degeneration in the *deaf* white cat commence in the upper half of the basal coil and extend longitudinally along the cochlear duct (Mair III). Degeneration of the spiral ganglion cells also shows a similar *spatial distribution*. Table 15 demonstrates that ganglion cell loss is first evident *in the upper basal coil* around the age of ten months, and this site of predilection remains the most severely affected, both extremities of the ganglion being relatively better preserved in the deaf adult. In the eight year deaf adult (Romeo), the neuron densities expressed as a percentage of the mean density per mm of the normal hearing cochlea are 1.6% in the *upper basal coil*, and respectively 15.3% and 19.2% in the hook region and at the apex. In the mouse *mutants* mentioned above, the spiral ganglion degeneration was found to commence in the "*basal half-turn*" and to spread along the duct *towards* the apex (Deol, 1954). Spiral ganglion *cell loss restricted* to the middle coil has been

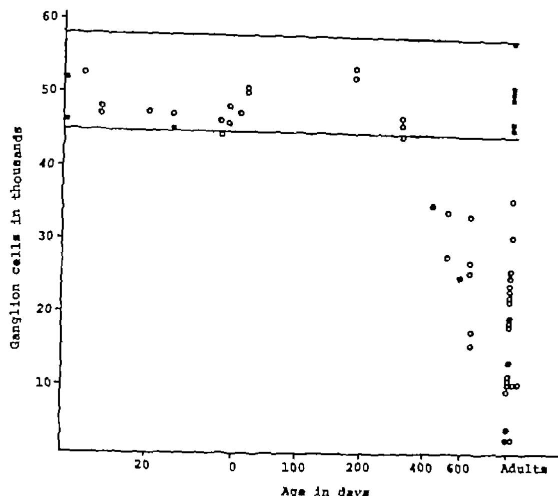


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The degeneration pattern of the structures in the cochlear duct of the deaf white cat has been previously shown to be closely related to the age of the animal (Mair III) Degeneration commences at the end of the first postnatal week progresses rapidly in the subsequent two to three weeks, and thereafter more slowly through

cells remain, and this figure is similar to the number of type II neurons. However the majority of the surviving neurons appear unhealthy and it seems not improbable that longer survival periods would reveal even lower ganglion cell counts. If this supposition is correct, then both type I and type II ganglion cells undergo degeneration following hereditary end-organ degeneration, although differing time patterns is a possibility. The distribution of the surviving ganglion cells, with considerably greater preservation at the apex and the hook region, would also appear to support this theory since the type II ganglion cells, which give rise to the basilar tunnel fibres (Spoendlin, 1972), have presumably a more or less constant density throughout the cochlea.

The presence of a slight degree of chromatolysis in some ganglion cells at the twenty day stage demonstrates that neuronal degeneration commences prior to hair cell loss. However significant loss of ganglion cells does not occur until one year later. Approximately 50% of the neurons survive at the end of the second year and thereafter the rate of ganglion cell loss slows down appreciably. The time pattern of cochlear degeneration in hereditary deafness is of prime importance in deciding the success or failure of electrode implantation in the treatment of human sensorineural hearing loss. Electrical stimulation by either perilymphatic or modiolar electrodes (Simmons & Glattke, 1972) is doomed to failure if the afferent neurons have already degenerated. Further study of cochlear end-organ and neuronal degeneration patterns in animals and man is therefore urgently required.

ZUSAMMENFASSUNG

Der Degenerationsprozess im Spiralganglion der erblich tauben weissen Katze wurde in verschiedenen Altersklassen quantitativ untersucht. Es wurden Cochleagang und Spiralganglion beim erblich und pathologisch veränderten Ohr mikroskopisch rekonstruiert, die durchschnittliche Länge des Spiralganglions betrug 10.67 mm und die durchschnittliche Gesamtzahl Neuronen betrug 51 770 beim funktionstüchtigen und histologisch normalen Ohr.

Ein Verlust an Spiralganglionzellen bei tauben Tieren trat statistisch signifikant erstmals nach 10 Monaten ein und nahm danach laufend weiter mit zunehmendem Alter ab. Der zentrale Ganglionabschnitt zeigte den grössten Verlust an Neuronen, während an beiden Enden des Rosenthalschen Kanals der Neuronenbestand rel. länger erhalten blieb.

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reported in the deaf dalmatian dog (Anderson et al 1968) and in the upper basal coil of the deaf Border collie (Igarashi et al 1972) The latter authors considered this region to be the most fragile part of the end-organ whilst Anderson et al. (1968) proposed that embryological factors might account for the preferential localisation of the degenerative process

Ruben (1967) has demonstrated by a radio-autographic study that the youngest cells of the organ of Corti are found in the basal coil and the oldest at the apex In the previously reported study of the cochlear histopathology in the white cat (Mair III) it was postulated that this aspect of the embryological development of the cochlea might help to explain the earlier occurrence of the degenerative process in the upper basal coil If this hypothesis is correct then neuronal degeneration is clearly secondary to hair cell degeneration since the oldest spiral ganglion cells are found in the basal and the youngest in the apical portions of the cochlea i.e the reverse of the arrangement in Corti s organ (Ruben 1967)

Degeneration of the more basal end of the spiral ganglion has been described in presbycusis (Schuknecht, 1955 Bredberg 1968), in hereditary human deafness (Beal et al 1967) and in presumed viral labyrinthitis (Lindsay Davey & Ward 1960) Apical coil degeneration occurs less frequently but has been reported in labyrinthine hydrops, both in the human (Kohut & Lindsay 1972) and in experimental material (Kimura, 1967) A similar apical spiral ganglion degeneration has been described in experimental obstruction of the labyrinthine vascular supply (Bernstein & Schuknecht, 1967) No abnormalities were found in the cochlear vascular system in the present series, and neither cochlear nor saccular hydrops was found to be a feature of the degenerative process. The markedly differing spiral ganglion degeneration patterns found in hydrops and in the hereditary deafness of the white cat may be additional evidence that volume oscillations of the endolymphatic duct due to hydrops are not typical of this degeneration process.

On the basis of experimental results from acute lesions to the organ of Corti it has for many years been maintained that spiral ganglion cell degeneration was secondary to loss of or damage to the supporting elements of Corti's organ primarily the pillar cells (Schuknecht, 1953 Spoendlin & Gacek, 1963) More recently a closer inter relationship has been demonstrated between inner hair cell loss and degeneration of the afferent neurons (Bredberg, 1968) A probable explanation for this latter theory is provided by the demonstration of two different cell populations in the spiral ganglion

Two types of ganglion cells have been previously reported in the spiral ganglion of the rat (Rosenbluth 1962) and the guinea pig (Kellerhals, Engstrom & Ades, 1967) but it was not until 1971 that a similar situation was demonstrated in the cat Spoendlin & Gacek (1963) had earlier transected the cochlear nerve in the internal auditory meatus and reported that the outer spiral fibres and terminals to the outer hair cells persisted despite degeneration of almost all the ganglion cells in Rosenthal s canal. Spoendlin (1971) re-examined the temporal bones from these transection experiments and found some neurons which had the morphological characteristics of type II ganglion cells This finding was then corroborated in an electron microscopy study of the ganglion in hearing animals

In the guinea pig no special relationship was found between the two types of ganglion cells and the inner and outer hair cells (Kellerhals et al 1967) whereas in the cat a specific innervation pattern was found (Spoendlin 1971) In the latter species, the type I cells, constituting 95 % of the total ganglion cell population innervate exclusively the inner hair cells and undergo retrograde degeneration following nerve section in the internal meatus On the other hand the type II cells are smaller considerably fewer in number only 5 % of the total, innervate mostly the outer hair cells, and apparently resist retrograde degeneration (Spoendlin 1971 1972)

In the oldest animal in the present series, Romeo eight years, only 6 of the ganglion

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Dedicated to

DR MORRIS B BENDER

teacher researcher and physician

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1 Introduction

Although the vestibular system has been extensively studied the function of the individual vestibular nuclei is still not clear (For reviews of recent and older studies see Camis & Creed 1930 Brodal et al 1962 Kornhuber 1966 Cohen 1971 Brodal & Pompeiano 1972) Moreover signs of lesions of individual vestibular nuclei or of parts of the vestibular nuclear complex are not well understood (Buchanan, 1940 Ferraro et al 1940 Scala & Spiegel 1941 Crammer 1951 Shanzer & Bender 1959 Abe 1960 Carpenter et al 1960) Four aspects of structural and functional organization have been demonstrated in recent studies

(1) Primary afferents from the semicircular canals and the otolith organs have a partially common and partially separate distribution in the vestibular nuclei (Lorente de Nó 1933 Stein & Carpenter 1967 Gacek 1969) The semicircular canals send axons mainly to the superior vestibular nucleus (SVN) the rostral medial vestibular nucleus (MVN) and the lateral vestibular nucleus (LVN) while the otolith organs project axons primarily to LVN caudal MVN and the descending vestibular nucleus (DVN) This implies that activity arising in the semicircular canals and otolith organs carrying information about angular head movements or about static head position and linear head movement is processed in different parts of the vestibular nuclei In apparent agreement with this neurons which respond to angular acceleration are mainly found in rostral portions of the vestibular nuclei while units which respond to head tilt occur more frequently in central and caudal portions of the vestibular nuclei (Adrian 1943 Duensing & Schaefer 1958 Shimazu & Precht 1965 Fujita et al 1968 Peterson 1970) Whether lesions in these regions would disturb semicircular canal or otolith organ function is not known

(2) Efferent vestibular pathways have been studied by a number of workers (Szentágothai 1950 1964 Brodal & Pompeiano 1957 *a* 1957 Brodal & Torvik, 1957 Carpenter et al 1959 Carpenter 1960 Brodal et al 1962 McMasters et al 1966 Tarlov 1969 1970 Gacek, 1971) SVN rostral MVN and ventral LVN receive primary afferent fibers from the semicircular canals and have direct connections to the eye muscle motor nuclei From this it has been inferred that these regions play an important role in mediating vestibulo-ocular reflexes from the semicircular canals An otolith organ projection has also been found in rostral MVN which in turn has connections to the oculomotor nucleus (Gacek, 1969 1971) Recently Highstein (1971 1973 *a*) Highstein and Ito (1971) and Highstein et al (1971) have shown that SVN mediates only inhibition in all of its known connections while rostral MVN mediates both excitation and inhibition (Baker et al. 1969 Highstein, 1973 *a b*). The effects of SVN rostral MVN and ventral LVN lesions on vestibulo-ocular reflexes are not known

(3) There are abundant connections between the vestibular nuclei on both sides of the brainstem According to Ladpli & Brodal (1968) these are separated into two groups One originates in the superior nucleus and the *ventral* parts of the other three main nuclei The other projection comes from the *descending* nucleus and ends chiefly in the ventral parts of the contralateral vestibular *nuclei*. Shimazu & Precht (1966) have shown the importance of commissural fibers in mediating crossed inhibition onto cells in the vestibular nuclei on the contralateral side.

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However there is little information about how eye movements would change if these fibers were interrupted

(4) Beyond the vestibular nuclei the separation of activity which arises in otolith organs and semicircular canals is maintained in many of the pathways through the pons and cerebellum to the oculomotor nuclei (see Carpenter 1971 Cohen 1971) How signs of lesions in the vestibular nuclei might differ from those of lesions in extra nuclear pathways is not known in many instances

The purpose of this research is to describe oculomotor changes produced by discrete lesions of the vestibular nuclei with the use of electro-oculography (EOG) By integrating these data with those from recent anatomic and physiologic studies it is hoped that a clearer idea of the function of the vestibular nuclei will emerge

2 Material and Methods

Thirty juvenile rhesus monkeys of 2 to 4 kg were used in these experiments. Animals were tested by using electro-oculography (EOG) to establish whether their spontaneous eye movements and induced nystagmus were normal (Komatsuzaki et al., 1969). Bipolar electrodes made of 0.25 mm insulated stainless steel wire with a 1 or 2 mm tip separation were introduced in horizontal stereotaxic planes into the region of the vestibular nuclei under anesthesia. Ocular responses to vestibular nuclei stimulation were used to aid in final placement of electrodes (Cohen et al., 1965 *a*; Tokumasu et al., 1969). Electrodes were cemented to the skull. Eye movements induced by electrical stimulation were observed after operation. The animals were also retested to determine effects of implantation on vestibulo-ocular reflexes.

Lesions were made by passing 5–10 mA of current through one or both of the electrodes for 15–60 seconds. Except where specified lesions were all on the left. Eye movements were observed and recorded by using EOG and cinematography. Animals were also photographed while sitting or climbing. They were tested until recovery or until there was no further change in vestibulo-ocular reflexes on several test occasions. The labyrinth on the side contralateral to the lesion was usually destroyed. This was done in order to selectively stimulate the labyrinth on the lesion side with positional tests. The cristae and nerves of the anterior, lateral and posterior semicircular canals, and the maculae and nerves of the utricle and saccule were identified and removed using an operating microscope. Animals were retested for another month.

Monkeys were killed with an overdose of barbiturates, and were perfused through the heart with saline and 10% formalin. After fixation in formalin, the brainstem and cerebellum were removed from the skull, embedded in celloidin, and sectioned in vertical stereotaxic planes. Alternate 40 µm sections were stained with cresyl violet and Weil stains. The lesions were drawn and photographed. Diagrams of representative sections through the vestibular nuclei in vertical stereotaxic planes separated by 0.5 mm are shown in Fig. 1. Microphotographs of representative sections through the vestibular nuclei 1.5 mm apart are shown in Fig. 2. The four main vestibular nuclei (Brodal & Pompeiano, 1957 *b*) and surrounding structures are labelled in these sections.

Techniques of electro-oculography (EOG)

Monkeys were tested while restrained in a primate chair. Animals received amphetamine sulfate (0.5 mg/kg) 30 min before testing to maintain a constant level of alertness. Horizontal and vertical eye movements were recorded using platinum needle electrodes inserted in the skin around the eyes. The horizontal EOG was registered binocularly from electrodes at the outer canthus of each eye using d.c.-coupling. The vertical EOG was a monocular recording from electrodes above and below each eye. It was taken using r.c. coupling with a 5 sec time constant. The EOGs were registered on an oscillograph and recorded on FM magnetic tape. The EOG was differentiated by amplifiers with a 3 msec time constant to obtain the velocity of eye movements. The differentiated EOG was rectified and amplified to measure the velocity of slow phases of nystagmus. Slow phase velocity was integrated to determine total

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Fig. 2. Representative sections through the rostral (*top*), central (*middle*), and caudal (*bottom*) portions of the left vestibular nucleus of a normal monkey. The major subdivisions and adjacent structures are shown in the diagrams on the right. They correspond to sections C, F and I of Fig. 1 and are separated by 1.5 mm. Cresyl violet (1st column) and Weil (2nd column) stains.

deviation of the eyes. In all figures eye movements to the right or upward cause upward pen movements.

The EOG was calibrated by having the animal look between lights 15° and 30° apart alternately turned on and off, or from slow phase velocity during OKN (Aschoff & Cohen, 1971). It was assumed that normal animals followed the OKN drum accurately at velocities up to 60°/sec. The calibration of the EOG was done in the normal animal and was assumed not to change during the period of observation. The calibration of the EOG varies in light and darkness. However, each animal was tested under similar conditions before and after operation so that the results were comparable, even if the EOG calibrations in darkness were approximate. Generally 22° of deviation caused about 1 mV of pen deflection in the EOG.

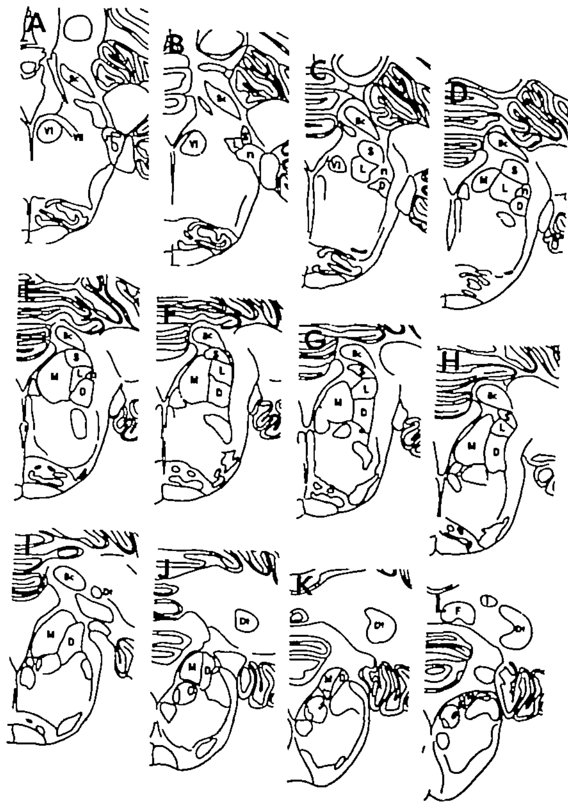


Fig 1 Diagrams of sections in the vertical stereotaxic plane through the left vestibular nuclei of a normal monkey The sections are 0.5 mm apart, and extend from the most rostral (A upper left) to most caudal (L lower right) parts of the nuclei. *VI* Abducens nucleus *VII* Facial nerve *n* Vestibular nerve *S* Superior vestibular nucleus *M* Medial vestibular nucleus *L*, Lateral vestibular nucleus *D* Descending vestibular nucleus *Bc* Brachium conjunctivum *Dt* Dentate nucleus *F* Fastigial nucleus *I* Interpositus nucleus

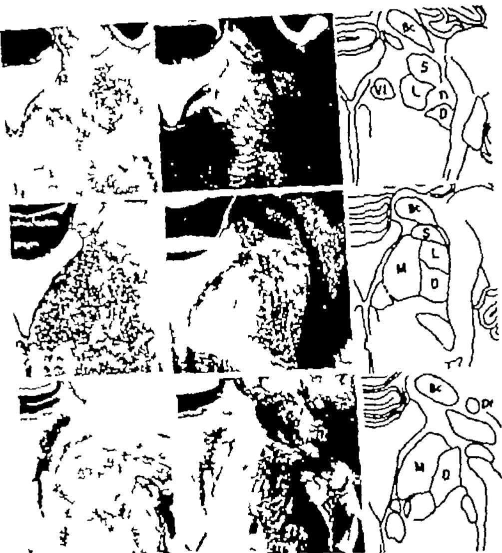


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Examinations which were performed included tests for·

1 *Spontaneous nystagmus and positional nystagmus* Animals were tested for spontaneous nystagmus seated upright in light and in darkness The direction of nystagmus was designated by the direction of the quick phases Left and right refer to the animal s left or right Clockwise or counterclockwise rotation is designated from the point of view of the observer

To elicit positional nystagmus animals were placed on their right and left sides and upside down in light and in darkness Nystagmus was recorded by EOG and was observed with the monkey behind Frenzel glasses Animals were moved to the upright position after each test in lateral or upside-down positions

Interpretation of positional nystagmus

Not all nystagmus recorded in the various head positions was considered to be of equal significance as an index of abnormality in utriculo-ocular or sacculo-ocular reflex arcs. If positional nystagmus was elicited *de novo* or if it differed from the spontaneous nystagmus the lesion was considered to have had an important effect on otolith-ocular reflexes. An example of this would be apogeotropic or geotropic direction-changing positional nystagmus In apogeotropic nystagmus the quick phases are in the opposite direction to gravity (i e. to the right with the left side down and vice versa) During geotropic nystagmus the quick phases are directed toward the ground (i e. to the left with the left side down and vice versa) On the other hand, if the provoked nystagmus was similar to the spontaneous nystagmus but was only of different intensity the lesion was considered to have had a less significant effect on otolith-ocular reflexes An example would be direction-fixed positional nystagmus associated with spontaneous nystagmus in the same direction The persistence or fatigability of positional nystagmus was also noted.

2 *Caloric nystagmus* Caloric nystagmus was induced by injecting 15 ml of water into the external auditory canals over a 15 sec period The induced nystagmus was recorded in darkness In some instances it was observed in light and photographed Water temperatures of 27°C and 47°C were used most often for caloric stimulation These are 10°C below and above the monkey s body temperature

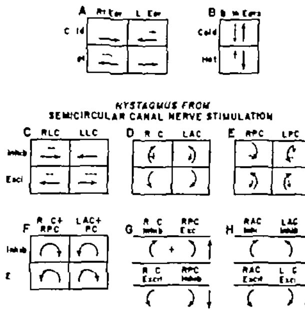


Fig 3 Directions of nystagmus which would be expected during unilateral (A) or bilateral (B) caloric stimulation or during excitation and inhibition of activity in semicircular canal nerves (C H). C–E show nystagmus from single semicircular canal stimulation and F G from simultaneous stimulation of both anterior and posterior canal nerves on one side. *H* is the nystagmus induced by bilateral anterior canal nerve excitation or inhibition and corresponds to the nystagmus shown in *B* *The thin dotted arrows show the direction of eye* movement during slow phases of nystagmus. The heavy *solid arrows show the direction of the quick phases.* The arrows representing the slow phases have been omitted from F–H The nystagmus is represented as seen by the observer i.e ← is nystagmus with slow phases to the animal s right and quick phases to the animal's left *RAC* right anterior canal *LAC* left anterior canal *RLC* right lateral canal *LLC* left lateral canal *RPC* right posterior canal *LPC* left posterior canal

During caloric irrigation the head was extended so that the horizontal canals were approximately in the vertical plane The animals were also stimulated when upside down with the horizontal canals vertical To induce vertical nystagmus both ears were stimulated simultaneously with hot or with cold water with the animals upright. To evaluate caloric nystagmus the direction was noted and the duration maximum slow phase velocity and total deviation were measured Maximum slow phase velocity was defined as the mean of 10 beats with the highest velocity

Interpretation of horizontal caloric nystagmus

With animals upright, stimulation of one ear with cold water induces nystagmus to the contralateral side which is mainly horizontal, and stimulation with hot water causes the opposite reaction. With animals upside down the horizontal component induced by stimulation with cold water is the reverse of that in the upright position due to reversal of convection currents in the endolymph. However vertical and rotatory components are enhanced when the animal is upside down.

By comparing nystagmus induced by caloric stimulation to nystagmus induced by electrical stimulation of individual semicircular canal nerves (Fig. 3 Suzuki et al., 1964, Suzuki & Cohen, 1964 Cohen et al., 1965 *b*), it is possible to infer whether there had been an increase or decrease in neural activity in the ampullary nerves during caloric stimulation. The caloric responses from stimulation of either ear with hot or cold water are shown in Fig. 3A. Nystagmus induced by increasing activity in the individual semicircular canal nerves (excitation) is shown in Fig. 3C–E, Excit. The dotted arrows show the direction of the tonic deviations or slow phases of nystagmus and the solid arrows the direction of the quick phases of nystagmus. The reverse nystagmus would be expected from reduction of activity in these nerves (inhibition) (Fig. 3C–E, Inhib.).

From comparison of Fig. 3A and 3C it can be inferred that ipsilateral nystagmus induced by hot stimulation is due to an increase in activity in the ampullary nerves and contralateral nystagmus induced by cold caloric stimulation is due to decrease in activity. This is true with the animal in the upright position. The reverse would hold during caloric stimulation with the animal upside down.

(2) If unilateral caloric stimulus had caused a simultaneous decrease of activity in one anterior canal nerve and an increase in the posterior canal nerve or vice versa, the expected nystagmus would be straight up or down without rotatory components (Fig. 3G). However if unilateral caloric stimulation induces any response other than horizontal it is usually primarily rotatory and vertical components are much less prominent. Moreover pure vertical nystagmus is never produced by unilateral stimulation. Thus it seems unlikely that a unilateral caloric stimulus simultaneously affects two vertical canals on the stimulated side in any combination.

(3) The single vertical canal most likely to be affected by caloric stimulation is the anterior canal. It lies close to the ear drum, and would be stimulated concurrently with the lateral canal. The posterior canals lie deeper in the middle ear farther from the drum. From the preceding argument, we would postulate that upward nystagmus caused by bilateral cold irrigation (Fig. 3B, Cold) is due to inhibition of activity in the nerves of both anterior canals (Fig. 3H Inhib) and downward nystagmus induced by bilateral hot irrigation (Fig. 3B Hot) is due to excitation in these same nerves (Fig. 3H Excit). If the preceding arguments are correct, there is little effect of the caloric stimulus on the posterior canals.

Although both anterior and lateral canals must be simultaneously activated by single caloric stimulus, the horizontal response predominates. Only when the horizontal canal responses are mutually inhibited as during bilateral stimulation do the anterior canal responses become manifest. Other evidence that the horizontal and anterior canals are mainly responsible for caloric nystagmus will be considered subsequently in the General Discussion (Chapter 10).

Interpretation of vertical caloric nystagmus

Bilateral simultaneous cold caloric stimulation causes upward nystagmus in the mid-sagittal plane and bilateral hot stimulation, downward nystagmus (Fig. 3B). This nystagmus is normally very intense in the monkey. There is no rotatory component to the vertical nystagmus when the eyes are in the mid-position. It is possible to infer which canals produce the vertical response by comparison with the results of electrical stimulation.

(1) When the anterior and posterior semicircular canal nerves on one side are electrically excited, the eyes tort or roll without much upward or downward component (Fig. 3F). If all four vertical canals are electrically excited, there is no eye movement (Cohen et al., 1964). Thus the vertical nystagmus induced by bilateral hot or bilateral cold stimulation could not have been induced by simultaneous excitation nor simultaneous inhibition of all four vertical canals. Therefore the anterior and posterior canal nerves on one side could not have been simultaneously excited or inhibited during unilateral caloric stimulation. Either activity was increased in one canal nerve (excitation) and decreased in the other (inhibition), or only one vertical canal was affected.

3 *Optokinetic nystagmus (OKN)* Optokinetic nystagmus (OKN) was induced by a servo-controlled optokinetic drum which surrounded the animal, and filled its field of vision. Four speeds of drum rotation were commonly used for testing: 45°/sec, 63°/sec, 90°/sec and 135°/sec. Monkeys were stimulated for 60 sec at each velocity. Mean maximum slow phase velocity was used to determine the intensity of OKN in a particular direction. To test for optokinetic after-nystagmus (OKAN), OKN was induced by drum rotation at 60°/sec or 90°/sec for 30 sec. The the lights were extinguished and OKAN was recorded in darkness.

4 *Positional alcohol nystagmus (PAN)* After alcohol ingestion animals were tested

Examinations which were performed included tests for

1 *Spontaneous nystagmus and positional nystagmus* Animals were tested for spontaneous nystagmus seated upright in light and in darkness The direction of nystagmus was designated by the *direction of the quick* phases Left and right refer to the animal s left or right Clockwise or counterclockwise rotation is designated from the point of view of the observer

To elicit positional nystagmus animals were placed on their right and left sides and upside down in light and in darkness Nystagmus was recorded by EOG and was observed with the monkey behind Frenzel glasses Animals were moved to the upright position after each test in lateral or upside-down positions

Interpretation of positional nystagmus

Not all nystagmus recorded in the various head positions was considered to be of equal significance as an index of abnormality in utriculo-ocular or sacculo-ocular reflex arcs. If positional nystagmus was elicited *de novo* or if it differed from the spontaneous nystagmus, the lesion was considered to have had an important effect on otolith-ocular reflexes. An example of this would be apogeotropic or geotropic direction-changing positional nystagmus In apogeotropic nystagmus the quick phases are in the opposite direction to gravity (i e to the right with the left side down and vice versa) During geotropic nystagmus the quick phases are directed toward the ground (i e. to the left with the left side down and vice versa).On the other hand if the provoked nystagmus was similar to the spontaneous nystagmus but was only of different intensity the lesion was considered to have had a less significant effect on otolith-ocular reflexes. An example would be direction-fixed positional nystagmus associated with spontaneous nystagmus in the same direction The persistence or fatigability of positional nystagmus was also noted.

2 *Caloric nystagmus* Caloric nystagmus was induced by injecting 15 ml of water into the external auditory canals over a 15 sec period The induced nystagmus was recorded in darkness In some instances it was observed in light and photographed Water temperatures of 27°C and 47°C were used most often for caloric stimulation These are 10°C below and above the monkey s body temperature

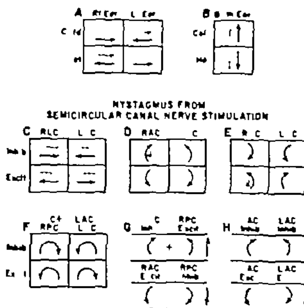


Fig 3 Directions of nystagmus which would be expected *during unilateral (A) or bilateral (B)* caloric stimulation or during excitation and inhibition of activity in semicircular canal nerves (C–H). C–E show nystagmus from single semicircular canal stimulation and F G from simultaneous stimulation of both anterior and posterior canal nerves on one side H is the nystagmus induced by bilateral anterior canal nerve excitation or inhibition and corresponds to the nystagmus shown in B The thin dotted arrows show the direction of eye movement during slow phases of nystagmus The heavy solid arrows show the direction of the quick phases. The arrows representing the slow phases have been omitted from F–H The nystagmus is represented as seen by the observer I.e → is nystagmus with slow phases to the animal s right and quick phases to the animal s left. *RAC* right anterior canal *LAC* left anterior canal *RLC* right lateral canal *LLC* left lateral canal *RPC* right posterior canal *LPC* left posterior canal

During caloric irrigation the head was extended so that the horizontal canals were approximately in the vertical plane The animals were also stimulated when upside down with the horizontal canals vertical To induce vertical nystagmus both ears were stimulated simultaneously with hot or with cold water with the animals upright To evaluate caloric nystagmus the direction was noted and the duration maximum slow phase velocity and total deviation were measured Maximum slow phase velocity was defined as the mean of 10 beats with the highest velocity

down. About 5 hours later the nystagmus reverses in most monkeys becoming apogeotropic direction-changing positional nystagmus (PAN II). In apogeotropic or antigravity nystagmus the quick phases are away from ground, being to the right with the left side down and vice versa. PAN II was not studied in these experiments.

PAN was recorded in darkness. The slow phases of the nystagmus were integrated to determine the total deviation of the eyes over 20 sec periods. If monkeys had spontaneous or positional nystagmus the intensity of PAN was estimated by adding or subtracting the intensity of this nystagmus to the PAN. Fig. 5 shows the reproducibility of intensity of PAN on two occasions.

Changes in posture. Oculomotor changes were of primary interest in this study but postural effects were also noted. Animals were photographed one or several days after lesions when sitting upright or attempting to sit upright, and when climbing on a bar. These postures are shown in appropriate places in the text and are summarized in Fig. 58 in the General Discussion.

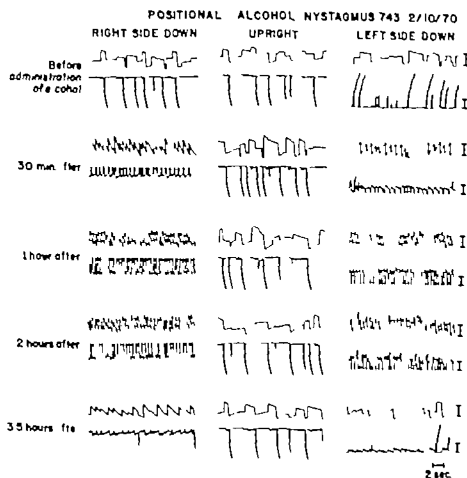
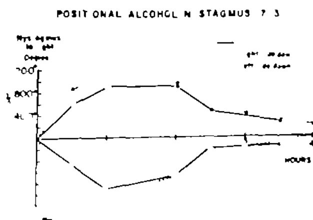


Fig 4 Positional alcohol nystagmus of a normal monkey during the *first phase (PAN I)* The top trace in each pair is the horizontal EOG and the bottom trace the differentiated rectified EOG showing slow phase velocity The calibrations are the vertical bars which are ‿2° for the EOG and 45°/sec for the differentiated EOG

for spontaneous nystagmus gaze nystagmus and positional nystagmus in lateral and upside down positions (PAN) PAN was used as a measure of the integrity of utriculo-ocular and sacculo-ocular pathways Monkeys were not fed before receiving alcohol and received the usual alerting dose of amphetamine (0 5 mg/kg) Pure ethanol (1 5 gm/kg) diluted 1 2 in water was introduced through a oro gastric tube PAN was tested 0 5 1 and 3 hours after ingestion of alcohol In the first phase (PAN I) the nystagmus is geotropic direction-changing positional nystagmus which reaches maximum intensity in about 1–1 5 hours (Figs 4 5) In geotropic positional nystagmus the quick phases are toward the ground being to the right with the right side down and to the *left with the left side*



F g 5 Graph showing *total deviation of eyes (with rate)* at various times during PAN of Monkey 743 on two separate test occasions The points were determined by measuring the total deviation of the eyes (integrated slow phase velocity) during 20 sec of the most active positional nystagmus Time after ingestion of alcohol is shown on the abscissa

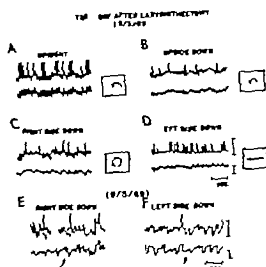


Fig 7 A–D, Spontaneous and positional nystagmus one day after left labyrinthectomy in 729 The upper trace in each pair is the vertical EOG and the lower trace the horizontal EOG The direction of the quick phases of nystagmus is shown in the diagram on the right. A, When the animal was upright, there was horizontal counter-clockwise rotatory spontaneous nystagmus to the contralateral side C, With the right side down the nystagmus was predominantly rotatory and D, with the left side down it was predominantly horizontal. B Counter-clockwise rotatory nystagmus was also found in the upside down position. E, F Positional nystagmus 3 days after left labyrinthectomy in 729 With the right side or left side down, there was horizontal component to the (left) ipsilateral side. This is indicated by the arrows below the bottom traces. The vertical bars show the calibration which is 15° for both the horizontal and vertical EOGs.

After labyrinthectomy ipsilateral OKAN initially disappeared and contralateral OKAN was decreased. For example the duration of OKAN was 44 sec to the right and left in 707 before right labyrinthectomy (Fig 8 A B) Four days after labyrinthectomy there was no OKAN to the ipsilateral side and only 13 sec of OKAN to the contralateral side Six days after operation the duration of OKAN was 3 sec to the ipsilateral (Fig 8 C) and 18 sec to the contralateral side (Fig 18 D). Findings were similar in 729

Alcohol (1.5 g/kg) induced positional alcohol nystagmus (PAN) to both sides after labyrinthectomy (Fig. 9 D F). The nystagmus was stronger to the contralateral side (Fig 9 F) However if the intensity of the spontaneous nystagmus (Fig. 9 E) was added to the PAN of Fig 9 D and subtracted from the PAN of Fig. 9 F then there was a relatively symmetrical effect of head position. This is shown by the graph of PAN after labyrinthectomy in Fig 10 (solid lines) In both monkeys the magnitude of changes in PAN was about half that of the original effect before labyrinthectomy

B *Bilateral labyrinthectomy* The second labyrinthectomy did not cause an ipsilateral head tilt in either monkey That is the head still remained slightly tilted to the side of the first labyrinthectomy (Fig. 6 B) There was some difficulty in holding the head upright, but no definite falling tendency to either side. Contralateral spontaneous nystagmus was present for 2 days in light and for about 1 week in darkness Spontaneous nystagmus was not affected by changes in head position before or after administration of alcohol (Fig. 9 G–I) but alcohol gaze nystagmus was still present.

OKN was initially somewhat asymmetrical after bilateral labyrinthectomy There was a decrease in the velocity of slow phases of ipsilateral OKN Moreover the animals could not follow well for OKN drum velocities above 60°/sec to either side for long periods of time (Cohen et al. 1973) OKAN could not be induced *after bilateral labyrinthectomy* in either animal although OKN was present (Fig. 8 E, F) The loss of OKAN after bilateral labyrinthectomy was permanent (Fig. 8 G H)

Comment

Signs after labyrinthectomy are similar to those reported previously (Magnus 1924 Northington & Barrera, 1934 Dow 1938) These included a head tilt and falling tendency toward the operated side a tendency to circle in that direction and spontaneous nystagmus toward the opposite side Recovery of postural asymmetry after unilateral labyrinthectomy

3 Labyrinthectomy

A *Unilateral labyrinthectomy* To provide a basis for comparing effects of central and peripheral vestibular lesions the labyrinths were destroyed in 2 animals (707 & 729) The results were similar in both monkeys After unilateral labyrinthectomy initially there was an ipsilateral head tilt (Fig 6 A) and the animals tended to fall toward the operated side The head tilt gradually recovered over about a month Dysequilibrium was not severe

There was horizontal rotatory nystagmus to the contralateral side in light for about 3 days in both animals After left labyrinthectomy the rotatory component of the spontaneous nystagmus was counterclockwise (Fig 7 A) Spontaneous nystagmus was present in darkness for 10 days in one animal and for more than 6 weeks in the other Although the predominant direction of the spontaneous nystagmus was contralateral (Fig 7 A–D) an ipsilateral horizontal component was present in the EOG 3–6 days after operation in both animals (Fig. 7 E F upward arrows) However ipsilateral horizontal nystagmus was not observed in light or behind Frenzel glasses

Changes in head position affected the spontaneous nystagmus after unilateral labyrinthectomy There was prominent contralateral horizontal nystagmus when the ipsilateral side was down (Fig 7 D) and rotatory nystagmus when the contralateral side was down (Fig 7 C) or when the animal was upside down (Fig 7 B)

OKN was induced in both directions after unilateral labyrinthectomy (Fig 8 C D) The velocity of the slow phases was initially less when the OKN was toward the ipsilateral side (Fig 8 C upward arrow) Directional preponderance persisted for about 2 weeks and was most prominent at higher drum velocities (≥90°/sec) After the directional preponderance disappeared the animal was unable to follow well at higher OKN drum velocities in either direction A more complete description of changes in OKN after labyrinthectomy is given elsewhere (Cohen et al 1973)

Optokinetic after-nystagmus (OKAN) is prominent in the monkey and persists for about 45–60 sec after the lights have been extinguished It is marked by the arrows in Fig 8 A B The direction of OKAN is the same as that of the OKN which preceded it



Fig 6 A Postural changes in Monkey 729 after left labyrinthectomy The head was tilted to the left. B After right labyrinthectomy the animal's head was still tilted slightly to the left side

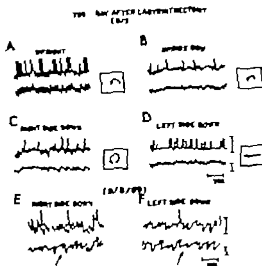


Fig. 7. A–D. Spontaneous and positional nystagmus one day after left labyrinthectomy in 729. The upper trace in each pair is the vertical EOG and the lower trace the horizontal EOG. The direction of the quick phases of nystagmus is shown in the diagram on the right. A, When the animal was upright, there was horizontal counter-clockwise rotatory spontaneous nystagmus to the contralateral side. C. With the right side down the nystagmus was predominantly rotatory and D. with the left side down it was predominantly horizontal. B. Counter-clockwise rotatory nystagmus was also found in the upside down position. E, F. Positional nystagmus 3 days after left labyrinthectomy in 729. With the right side or left side down, there was horizontal component to the (left) ipsilateral side. This is indicated by the arrows below the bottom traces. The vertical bars show the calibration which is 10° for both the horizontal and vertical EOGs.

After labyrinthectomy ipsilateral OKAN initially disappeared and contralateral OKAN was decreased. For example the duration of OKAN was 44 sec to the right and left in 707 before right labyrinthectomy (Fig. 8 A, B). Four days after labyrinthectomy there was no OKAN to the ipsilateral side and only 13 sec of OKAN to the contralateral side. Six days after operation the duration of OKAN was 3 sec to the ipsilateral (Fig. 8 C) and 18 sec to the contralateral side (Fig. 18 D). Findings were similar in 729.

Alcohol (1.5 g/kg) induced positional alcohol nystagmus (PAN) to both sides after labyrinthectomy (Fig. 9 D, F). The nystagmus was stronger *to the contralateral* side (Fig. 9 F). However, if the intensity of the spontaneous nystagmus (Fig. 9 E) was added to the PAN of Fig. 9 D and subtracted from *the PAN of* Fig. 9 F, then there was a relatively symmetrical effect of head position. This is shown by the graph of PAN after labyrinthectomy in Fig. 10 (solid lines). In both monkeys the magnitude of changes in PAN was about half that of the original effect before labyrinthectomy.

B. Bilateral labyrinthectomy. The second labyrinthectomy did not cause an ipsilateral head tilt in either monkey. That is, the head still remained slightly tilted to the side of the first labyrinthectomy (Fig. 6 B). There was some difficulty in holding the head upright, but no definite falling tendency to either side. Contralateral spontaneous nystagmus was present for 2 days in light and for about *1* week in darkness. Spontaneous nystagmus was not affected by changes in head position before or *after administration of* alcohol (Fig. 9 G–I), but alcohol gaze nystagmus was still present.

OKN was initially somewhat asymmetrical after bilateral labyrinthectomy. There was a decrease in the velocity of slow phases of ipsilateral OKN. Moreover, the animals could not follow well for OKN drum velocities above 60°/sec to either side for long periods of time (Cohen *et al.* 1973). *OKAN* could not be induced after bilateral labyrinthectomy in either *animal, although OKN was present* (Fig. 8 E, F). The loss of OKAN *after bi*lateral labyrinthectomy was permanent (Fig. *8 G, H*).

Comment

Signs after labyrinthectomy are similar to those *reported* previously (Magnus 1924, *Northington & Barrera,* 1934, Dow 1938). *These included* a head tilt and *falling* tendency toward the operated side, a tendency to circle in that direction and *spontaneous nystagmus toward* the opposite side. Recovery of postural *asymmetry* after unilateral labyrinthectomy

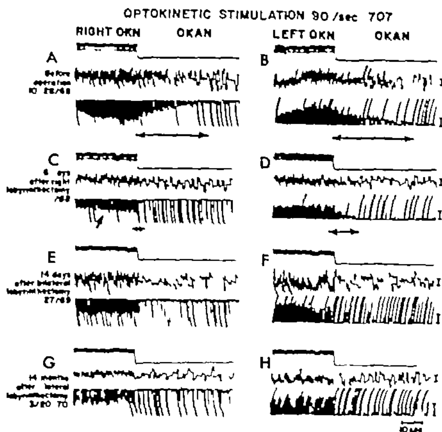


Fig 8 OKN and OKAN before operation (A B) after right labyrinthectomy (C D), and after bilateral labyrinthectomy (E–H) The upper trace in each part records the passage of drum stripes during OKN At the end of stimulation the lights were extinguished and the animal was in darkness for the remainder of the tracing The second trace is the horizontal EOG The third trace shows slow phase velocity The duration of OKAN is marked in A–D C D After right labyrinthectomy the monkey had OKN to both sides but there was a re tion in the maximum velocity of slow phases of (to the right (upward arrow). Note that OKAN markedly diminished after labyrinthectomy r E–F After bilateral labyrinthectomy n OKAN recorded G H Similar findings were recorde months later The calibrations are 16 for the l and 32°/sec for the slow phase velocity traces.

was almost complete within 1 month The second labyrinthectomy affected posture much less than the first operation

Spontaneous nystagmus was found in dark ness for long periods after unilateral laby rinthectomy The small but clear-cut ipsi lateral horizontal component found in the EOG at some time during the recovery course was also present in other animals when laby rinthectomy was done after vestibular nuclei lesions

The interaction between the vestibular and visual systems is se n in the effects of laby rinthectomy on OKN and OKAN Not only was there directional pr ponderance of OKN to the contralateral side after labyrinth ectomy but the animals were unable to follow the OKN drum well to the either sid higher velocities Moreover OKAN v markedly diminished after unilateral la rinthectomy and permanently lost after lateral labyrinthectomy This suggests that peripheral labyrinths and the vestibu system play an important role in supporti production of certain visual-ocular reflex

PAN is permanently abolished after lateral destruction of the labyrinths (deKle & Versteegh 1930 Aschan et al 196 However alcohol gaze nystagmus (Asch et al 1956) persists even after bilater labyrinthectomy (Harris et al 196?)

There is disagreement as to whether or n PAN is present to both sides after unilater labyrinthectomy In acute experiments it wa

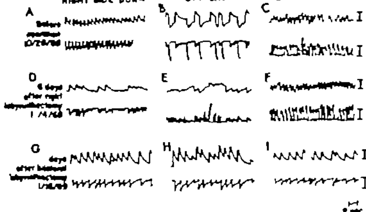


Fig 9 Positional alcohol nystagmus and labyrinthectomy in 707 The upper trace is the horizontal EOG and the lower trace the slow phase velocity Before operation there was active nystagmus t the right with the right side down (A) and to the left with the left side down (C) Six days after right labyrinthectomy there was spontaneous nystagmus to the left in the upright position (E). Weak positional nystagmus was induced to the right i the right side down position (D) and strong positional nystagmus to the left in the left side down position (F). Four days after left (bilateral) labyrinthectomy there was spontaneous nystagmus to the right (H) which was unchanged in either right side down (G) or left side down (I) positions. The vertical bars beside the EOGs show the calibration which is 16° for the horizontal EOG and 32°/sec for the slow phase velocity traces.

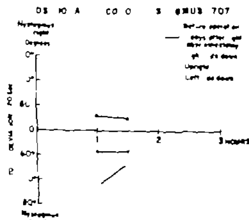


Fig 10 Graph of intensity of PAN I in 707 before (→) and after (←→) right labyrinthectomy Before labyrinthectomy the magnitude of the response was symmetrical to both sides. After labyrinthectomy there was spontaneous nystagmus during which the eye deviated about 150° to the left during 20 seconds. The magnitude of the change in the spontaneous nystagmus was approximately symmetrical during PAN

not present when the operated side was down (deKleijn & Versteegh 1930) However Aschan et al (1964) demonstrated it in a human subject 10 years after removal of a neurinoma with destruction of the vestibular nerve PAN I was present in monkeys in both directions after unilateral labyrinthectomy

The magnitude of PAN determined by adding the nystagmic responses in the right and left side down position before operation was decreased to about half after unilateral labyrinthectomy It would appear that the otolith organs on each side sense gravitational forces or linear acceleration almost equally in both directions and that about half of the ocular response is caused by each of them The semicircular canals also sense angular acceleration equally well in either direction after unilateral labyrinthectomy and the intensity of the ocular response to rotation is reduced by about half (Niven & Graybiel 1953 Money & Scott 1964)

4 Lesion of the Root Entry Zone

The left vestibular nerve was partially de stroyed at the ventrolateral border of the LVN in Monkey 728 Diagrams through the lesion are shown in Fig 11 The lesion was about 2 5 mm long and 1 mm wide It lay in the middle portion of the vestibular nerve (Fig 11 B–D) and grazed the rostral end of DVN (Fig 11 D–F) As shown in Fig 11 C and Fig 12 there was demyelination and gliosis extending throughout the ventro-medial por tion of LVN (smaller cell area) There was also some fiber loss in the most rostral por tions of DVN (Fig 11 E) No significan gliosis was present in other parts of DVN in SVN or in the dorso-lateral portion (gran cell area) of LVN

Stimulation through the implanted electrod prior to lesion produced horizontal clockwis rotatory movements of the eyes to the ipsi lateral side (⌒) The quick phases o nystagmus induced by repetitive stimulatio were in the same direction as eye movement

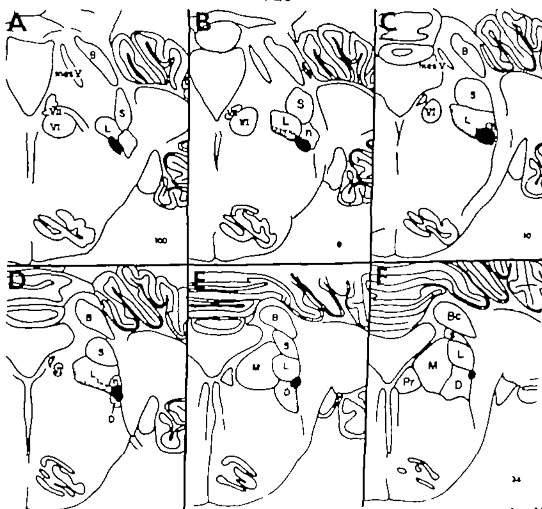


Fig 11 Diagram showing the lesion (black) and area of demyelination and gl osis (st ppled) in 728 The sec tions which are shown extend over about 1.5 mm in the rostro-caudal direction *mes V* Mesencephalic trige minal nucleus *Pr* Nucleus praepositus hypoglossi



Fig. 12 Microphotographs of Section C Figure 11 showing the demyelination (A) and gliosis (B) in ventral portions of LVN after destruction of portion of the vestibular nerve root. The degeneration did not extend into the rostrodorsal (giant cell) area of LVN

induced by stimulation of this region with pulse trains After lesion there was a persistent head tilt (Fig 13 A) and a tendency to fall to the ipsilateral side The head tilt and falling tendency were somewhat stronger than in monkeys with unilateral labyrinthectomy (Fig. 6 A)

Spontaneous and positional nystagmus The spontaneous nystagmus was initially contralateral with a small counterclockwise rotatory component (Fig. 14 A). It was opposite in direction to the nystagmus induced by repetitive stimulation before lesion It persisted for 3 days in light and for 1 week in darkness

Lateral head positions were effective in inducing nystagmus throughout the animal's recovery course Initially contralateral counter clockwise rotatory nystagmus was induced when the opposite side was down (Fig 14 C) Later this nystagmus disappeared but there was downward nystagmus when the ipsilateral (left) side was down.

OKN and OKAN OKN and OKAN were symmetrical in this animal before lesion. Six days after lesion there was directional

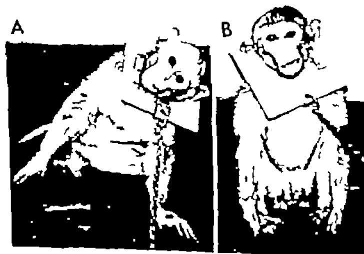


Fig. 13 A, Postural changes after nerve root lesion on left in 728 and B after contralateral (right) labyrinthectomy

4 Lesion of the Root Entry Zone

The left vestibular nerve was partially de stroyed at the ventrolateral border of the LVN in Monkey 728 Diagrams through the lesion are shown in Fig 11 The lesion was about 2 5 mm long and 1 mm wide It lay in the middle portion of the vestibular nerve (Fig 11 B–D) and grazed the rostral end of DVN (Fig 11 D–F) As shown in Fig 11 C and Fig 12 there was demyelination and gliosis extending throughout the ventro-medial por *tion of LVN (smaller cell area) There was* also some fiber loss in the most rostral por tions of DVN (Fig 11 E) No significant gliosis was present in other parts of DVN in SVN or in the dorso-lateral portion (giant cell area) of LVN

Stimulation through the implanted electrode prior to lesion produced horizontal clockwise rotatory movements of the eyes to the ipsi lateral side (⌒) The quick phases of nystagmus induced by repetitive stimulation *were in the same direction as eye movements*

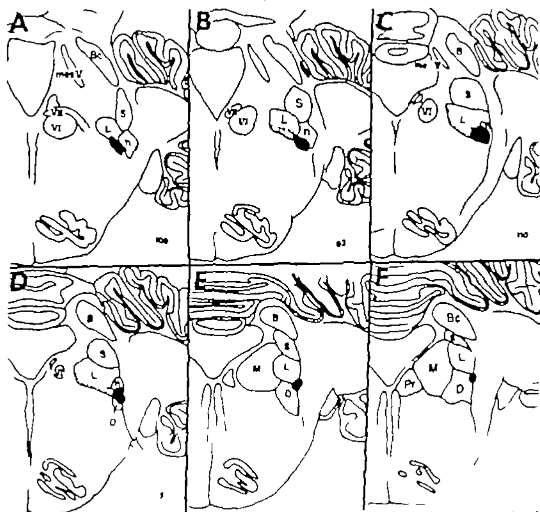


Fig 11 Diagram showing the lesion (black) and area of demyelination and gliosis (stippled) in 728 The sec tions which are shown extend over about 1.5 mm in the rostro-caudal direction *mes V* Mesencephalic trige minal nucleus *Pr* Nucleus praepositus hypoglossi



Fig. 12. Microphotographs of Section C, Figure 11 showing the demyelination (A) and gliosis (B) in ventral portions of LVN after destruction of portion of the vestibular nerve root. The degeneration did not extend into the rostrodorsal (giant cell) area of LVN

induced by stimulation of this region with pulse trains. After lesion there was a persistent head tilt (Fig. 13 A) and a tendency to fall to the ipsilateral side. The head tilt and falling tendency were somewhat stronger than in monkeys with unilateral labyrinthectomy (Fig. 6 A).

Spontaneous and positional nystagmus. The spontaneous nystagmus was initially contralateral with a small counterclockwise rotatory component (Fig. 14 A). It was opposite in direction to the nystagmus induced by repetitive stimulation before lesion. It persisted for 3 days in light and for 1 week in darkness.

Lateral head positions were effective in inducing nystagmus throughout the animal's recovery course. Initially contralateral counterclockwise rotatory nystagmus was induced when the opposite side was down (Fig. 14 C). Later this nystagmus disappeared but there was downward nystagmus when the ipsilateral (left) side was down.

OKN and OKAN. OKN and OKAN were symmetrical in this animal before lesion. Six days after lesion there was directional

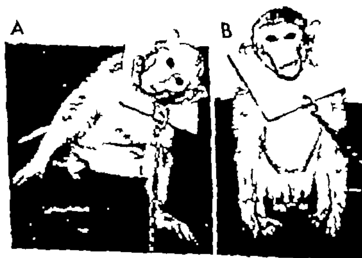


Fig. 13. A, Postural changes after nerve root lesion on left in 728, and B, after contralateral (right) labyrinthectomy

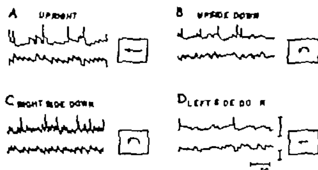


Fig 14 A–D Spontaneous and positional nystagmus in 728 one day after lesion The direction of the nystagmus is shown by the arrows beside the EOGs A When the animal was upright there was spontaneous horizontal nystagmus to the right. In right-side down (C) and upside down (B) positions the nystagmus was horizontal rotatory and in left-side down position (D), it was predominantly horizontal The upper trace in each pair is the vertical EOG and the lower trace the horizontal EOG The calibrations show 25° for both horizontal and vertical traces.

preponderance of OKN to the contralateral side This had almost disappeared by 14 days and by 40 days OKN was symmetrical OKAN was initially absent to the ipsilateral side and reduced to the contralateral side after lesion 40 days after the lesion the contra lateral OKAN had recovered but the ipsi lateral OKAN was still reduced

Caloric nystagmus The caloric response of the left ear was reduced after the lesion in 728 The defect was most apparent when water temperatures farther away from body temperature were used for stimulation For example when the right ear was stimulated 2 weeks after lesion there was a normal graded increase in maximum slow phase velocity dependent on the intensity of the stimu lus (Fig 15 right ear Fig 16 A solid lines) Stimulation of the left ear however induced nystagmus in whose maximum slow phase velocity did not increase along with increases in water temperature (Fig 15 left ear Fig 16 A dotted lines) Thus there was little or no recruitment when the intensity of the stimulus was increased Moreover the absolute value of the slow phase velocities induced at 27° and 17°C were lower after than before operation

The difference in the velocity of the slow phases of nystagmus induced by stimulation 10° above and below body temperature are marked in Fig 16 A by arrows There was a greater difference in the slow phase velocities induced by hot than by cold caloric stimula tion These findings are consistent with the interpretation that there was canal paresis on the left (lesion) side and directional pre ponderance of caloric nystagmus to the right An interesting feature of this nystagmus was that duration and maximum slow phase ve locity were affected differently There was little difference between the duration of ipsi- and contralateral caloric responses (Fig 16 B) although there was a distinct difference in the velocity of the slow phases (Fig 16 A)

PAN Monkey 728 was tested for PAN 15 days after lesion No spontaneous nystagmus was induced by alcohol and the animal had direction-changing positional nystagmus during PAN I The intensity of the nystagmus was somewhat greater to the right than to the left This probably reflected the right directional preponderance which was also present in caloric nystagmus and OKN

Right labyrinthectomy After right labyrinthectomy there was a slight head tilt and a weak falling tendency to the right (Fig 13 B) For a short period after right labyrinthectomy there was spontaneous nystagmus to the left in light This nystagmus was much more intense with the left side down It was present in darkness one week later At that time the spontaneous nystagmus had an ipsilateral horizontal component in the EOG similar to that found after unilateral laby rinthectomy at a similar time after lesion (Fig 7 E F)

7 and 22 days after right labyrinthectomy slow phases of OKN were of greater velocity when OKN was to the left than to the right OKAN was initially absent to the right and reduced to the left when compared with

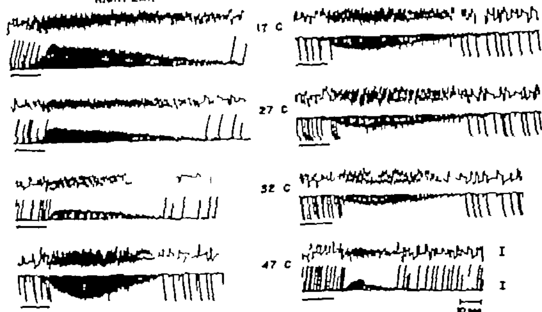


Fig. 15. Caloric nystagmus recorded 14 days after lesion in 728. The upper trace in each pair is the horizontal EOG and the lower trace shows slow phase velocity. The underlying horizontal bars show the duration of stimulation. At the end of stimulation the lights were extinguished and the rest of the recording was done in darkness. Notice that the nystagmus induced from the left ear by water temperatures of 17°C, 27°C, and 47°C was less intense than from the right ear. Nystagmus induced by water at 32°C was approximately symmetrical. The calibrations beside the lower right hand trace show 25° for the EOG and 50°/sec for the slow phase velocity trace.

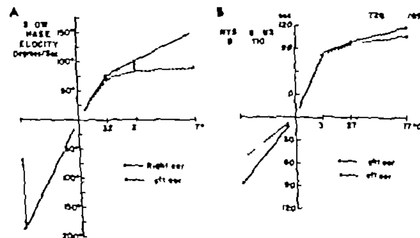


Fig. 16. Graphs of slow phase velocity (A) and duration (B) of the nystagmus shown in Fig. 15. Note the lower slow phase velocities induced by stimulation of the left ear (–). Note also the relatively limited increase in maximum slow phase velocity when water temperatures farther away from body temperature were used for stimulation of the left ear. There was not as much difference in duration of nystagmus induced from the two ears as in slow phase velocity. The arrows point to the differences in slow phase velocity which suggest directional preponderance to the right as well as canal paresis on the left.

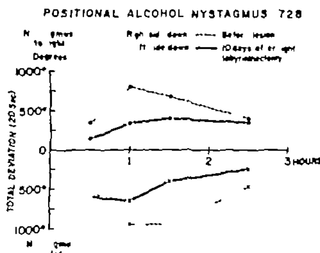


Fig 17 Total deviation during PAN I before lesion (- -) and 10 days after right labyrinthectomy (——)

OKAN recorded 40 days after the initial lesion Twenty two days after right labyrinthectomy the duration of OKAN was still shorter than before labyrinthectomy right > left

PAN was induced to both sides when tested *10 days after right labyrinthectomy (Fig 17* solid lines) The magnitude of the response during PAN *was about half that of the original response (Fig 17 dotted lines)*

Caloric nystagmus was induced by stimulation of the left ear 23 days after right labyrinthectomy The ipsilateral (left) nystagmus induced by stimulation with hot water (47°C) was now stronger than the contralateral (right) nystagmus induced by cold water (?7°C) Despite the reversal of directional preponderance of caloric nystagmus *produced by the* labyrinthectomy there was still no recruit*ment in the maximum* velocity of slow phases by increasing the intensity of stimulation

Comment

The only gross changes in the vestibular nuclei in 728 *were damage to the nerve root* and gliosis and fiber loss in the ventral portion of LVN The latter finding was *presumably* secondary to interruption of the afferent fibers from the labyrinth Findings in 7?8 were similar to those in animals with unilateral labyrinthectomy *(707 729) (1) head* tilt and falling tendency to the ipsilateral side (2) spontaneous nystagmus toward the contralateral intact side (3) an effect of head position on spontaneous nystagmus (enhancement of the rotatory component with the intact side down) and (4) decreased or *absent response to caloric testing i e canal* paresis on the side of the lesion One exception was that the postural asymmetry was somewhat stronger after the nerve root (7?8) than the peripheral labyrinthine lesions (707 & 729) It appeared that the symptoms in 728 were mainly due to damage of the vestibular nerve trunk at the root entry zone

Responses from both the semicircular canals and otolith organs were affected by *the* lesion in 728 since there were changes in calo*ric nystagmus and some positional effects on* the spontaneous nystagmus However the *most striking changes were in caloric nystagmus and consisted of a decrease in the veloc*ity of slow phases induced by stimulation of the ipsilateral ear and an inability of stronger caloric stimuli on the left to recruit stronger nystagmus Positional alcohol nystagmus was not much affected by the root entry zone *lesion in 728 After the contralateral laby*rinth was destroyed the magnitude of PAN *was reduced to about half* This is similar to changes in PAN in 707 and 729 after unilateral labyrinthectomy From this we would infer that the root entry zone lesion in 7?8 had not significantly interrupted primary afferents most probably from the otolith organs which produce PAN

5 Lesion of Rostral Descending Vestibular Nucleus

In 717 the main portion of the lesion was in rostral DVN on the right side (Fig 18 E F I) Diagrams and microphotographs of the lesion in Figs 18 and 19 were reversed to be compatible with those in other animals The postural and EOG findings were not reversed, but are shown as recorded. The lesion also damaged the caudal portion of the nerve root (Fig. 18 C) and the lateral and ventral-most portions of LVN (Fig 18 C–E 19 B C) Rostral-most parts of LVN remained intact (Fig. 18 A) In rostral LVN gliosis and fiber loss were limited to the ventral portions (Fig. 18 B) but were present in both ventral and dorsal portions of caudal LVN (Fig. 18 C D) Gliosis and fiber loss extended throughout DVN caudal to the lesion (Fig. 18 G H) The demyelination in caudal DVN on the lesion side can be seen by comparing it to DVN on the normal side (Fig. 19 D arrows) In the cerebellum there was gliosis and loss of myelinated fibers in the medial part of the ipsilateral fastigial nucleus (Fig. 18 E–H) MVN and SVN were not affected.

Stimulation with pulse trains through the implanted electrodes before lesion caused the eyes to move to the ipsilateral side (←) Horizontal rotatory nystagmus to the ipsilateral side was induced by repetitive stimulation (↶) After the lesion there was a strong head tilt and falling tendency to the ipsilateral side (Fig. 20 A) and some head

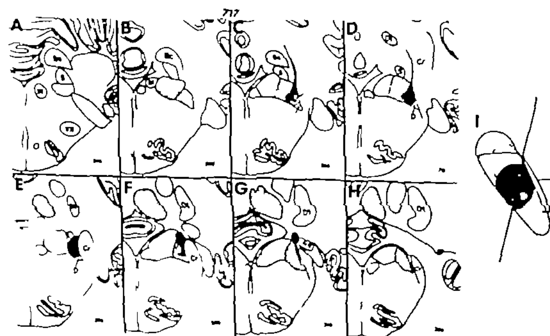


Fig 18 Diagrams of lesion (black) and areas of demyelination and gliosis (stippled) in 717 The extent of the lesion and of the degenerative changes are shown in I which is sagittal view of the vestibular nuclei from the lateral side. The vertical line shows the plane of section for A–H and for Fig. 19 *Cr* Restiform body *ch*l *N* Cochlear nerve.

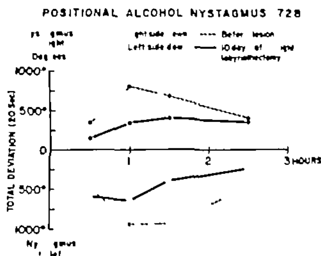


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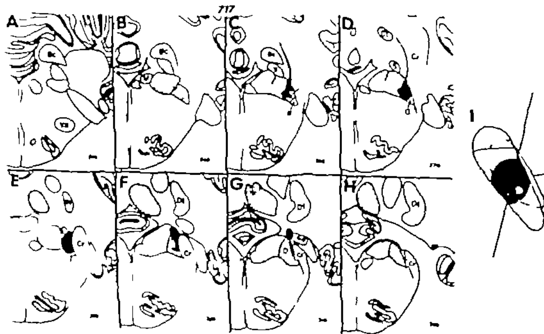


Fig 18 Diagrams of lesion (black) and areas of demyelination and gliosis (stippled) in 717 The extent of the lesion and of the degenerative changes are shown in I back in sagittal view of the vestibular nuclei from the lateral side. The vertical line shows the plane of section for A–H and for Fig. 19 C Restiform body *cN* N Cochlear nerve.

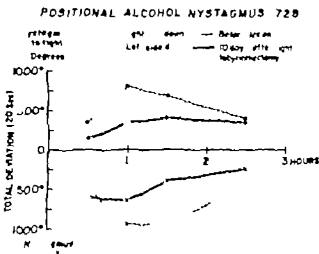


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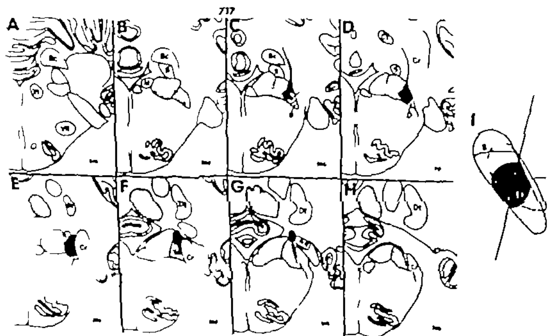


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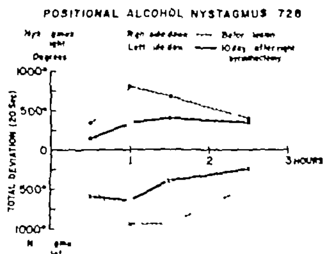


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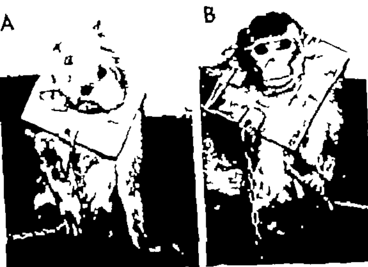


Fig 20. A. Head tilt to the ipsilateral (right) side after right DVN lesion in 717 The monkey also had some falling tendency to the right. B Head and body posture after left labyrinthectomy

22 23 A dotted lines) There was no difference in velocity of slow phases of nystagmus induced by hot stimulation of two ears (Fig. 22, 47°C 23 A arrows) Nystagmus duration was not of value in reflecting the side of the lesion in 717 since the duration of caloric nystagmus was longer after stimulation of the lesion side (Fig. 23 B solid lines right ear) than the intact side (Fig. 23 B dotted lines left ear)

PAN Administration of alcohol on the 12th day after lesion provoked strong spontaneous nystagmus to the ipsilateral (right) side (Fig 24 E, upright) Nystagmus to the right was enhanced when the ipsilateral (right) side was down (Fig. 24 D) and was inhibited when the contralateral (left) side was down (Fig. 24 F) On the 48th day there was also strong spontaneous nystagmus to the ipsilateral side (Fig 24 H upright) It was enhanced with the ipsilateral side down (Fig. 24 G) and reversed when the contralateral side was down (Fig. 24 I).

Left labyrinthectomy The left labyrinth was destroyed 71 days after lesion. After labyrinthectomy there was a slight head tilt to the left with some falling tendency to the left (Fig. 20 B) There was spontaneous nystagmus to the right after labyrinthectomy It was not affected by moving the head into either the right or left lateral position. On the 8th day after operation the spontaneous nystagmus was still present in darkness Administration of alcohol enhanced the spontaneous nystagmus (Fig. 24 K) but neither the right (Fig. 24 J) nor the left lateral positions (Fig. 24 L) had any effect on this nystagmus.

Associated with the strong spontaneous

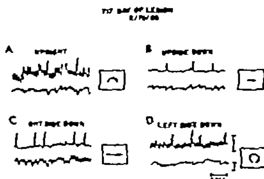


Fig 21 Spontaneous (A) and positional nystagmus shortly after lesion in 717 A, There was strong spontaneous rotatory nystagmus to the left. The nystagmus was predominantly horizontal with the lesion side (*right*) down (C) or upside down (B). With the left side down (D) the nystagmus was rotatory The vertical bars show 20° of deviation for the vertical (*upper trace*) and horizontal (*lower trace*) EOGs.

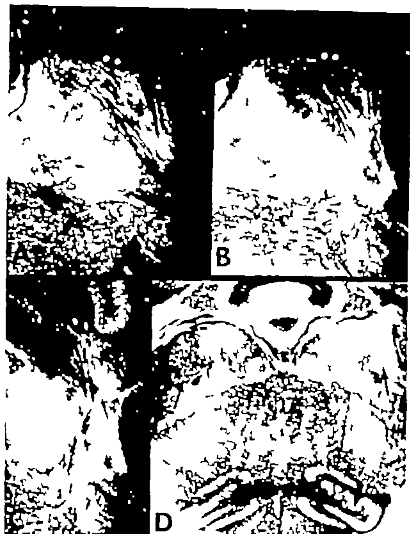


Fig 19 A–D Photomicrographs of destruction and demyelination in the vestibular nuclei in 717 Weil stain These sections correspond to or are close to the following diagrams in Fig. 18. A and Fig. 18 B B and Fig. 18 D C and Fig. 18 E and D and Fig. 18 G The arrows in D point to caudal DVN on both sides. Note the demyelination on the lesion side.

nystagmus The head tilt was more marked than that after labyrinthine destruction in 707 and 729 However the monkey was able to sit on the day of the lesion

Spontaneous and positional nystagmus Contralateral spontaneous nystagmus was present after lesion (Fig 21 A) It had strong clockwise rotatory and upward components and lasted for 8 days in light It was more persistent than in monkeys with unilateral labyrinthectomy 12 days later the horizontal component of the spontaneous nystagmus reversed

The effect of head position on the spontaneous nystagmus was similar to that after labyrinthectomy the horizontal component was enhanced when the ipsilateral side was down (Fig 21 C bottom trace) and the rotatory component was more prominent when the contralateral side was down (Fig 21 D) Later rotatory nystagmus appeared only when the contralateral (left) side was down

OKN and OKAN OKN was almost symmetrical to both sides by the 8th day after lesion OKAN was markedly diminished by the lesion ipsilateral>contralateral It had not recovered by 9 weeks after lesion

Caloric nystagmus Findings in 717 were similar to those in 728 in that more intense caloric nystagmus could not be recruited by applying stronger cold caloric stimuli to the ear on the side of the lesion Caloric nystagmus induced 2 months after lesion is shown in Fig 22 and analysed in Fig 23 The velocity of slow phases induced by cold stimulation was less from the right ear (Fig 22 23 A solid lines) than from the left ear (Fig

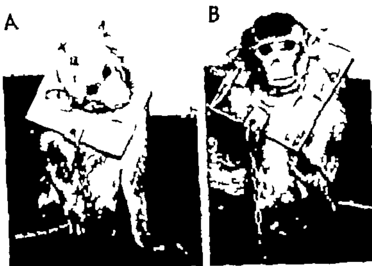


Fig. 20. A. Head tilt to the ipsilateral (right) side after right DVN lesion in 717. The monkey also had some falling tendency to the right. B. Head and body posture after left labyrinthectomy.

22, 23 A, dotted lines). There was no difference in velocity of slow phases of nystagmus induced by hot stimulation of two ears (Fig. 22, 47°C; 23 A, arrows). Nystagmus duration was not of value in reflecting the side of the lesion in 717 since the duration of caloric nystagmus was longer after stimulation of the lesion side (Fig. 23 B, solid lines, right ear) than the intact side (Fig. 23 B, dotted lines, left ear).

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Left labyrinthectomy. The left labyrinth was destroyed 71 days after lesion. After labyrinthectomy there was a slight head tilt to the left with some falling tendency to the left (Fig. 20 B). There was spontaneous nystagmus to the right after labyrinthectomy. It was not affected by moving the head into either the right or left lateral position. On the 8th day after operation the spontaneous nystagmus was still present in darkness. Administration of alcohol enhanced the spontaneous nystagmus (Fig. 24 K), but neither the right (Fig. 24 J) nor the left lateral positions (Fig. 24 L) had any effect on this nystagmus.

Associated with the strong spontaneous

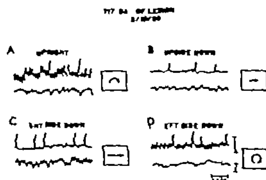


Fig. 21. Spontaneous (A) and positional nystagmus shortly after lesion in 717. A. There was strong spontaneous rotatory nystagmus to the left. The nystagmus was predominantly horizontal with the lesion side (right) down (C) or upside down (B). With the left side down (D) the nystagmus was rotatory. The vertical bars show 20° of deviation for the vertical (upper trace) and horizontal (lower trace) EOGs.

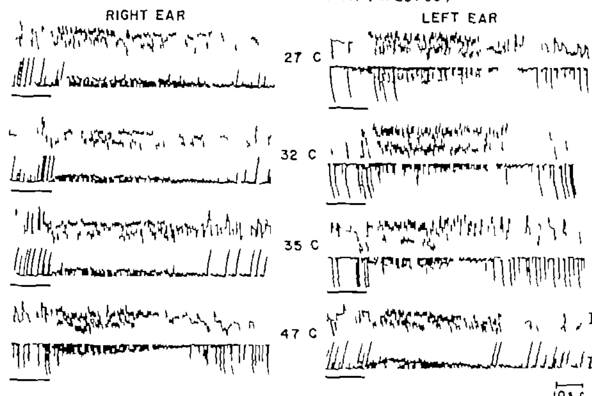


Fig 22 Nystagmus induced by caloric stimulation 2 months after lesion. The EOG is the upper trace and slow phase velocity is the lower trace The solid bars under the slow phase velocity trace show the duration of stimulation The lights were extinguished at the end of stimulation and the caloric nystagmus was recorded in darkness Note that the velocity of the slow phases induced by stimulating the right ear with cold water did not increase as the stimuli were made more intense The vertical bars are ?0° for the horizontal EOG and 80°/sec for the slow phase velocity traces

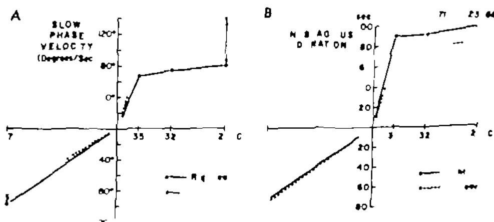


Fig 23 Graphs of slow phase velocity (A) and duration (B) of nystagmu induced by caloric stimulation *2 months after lesion 717 The lesion side is the right* (—) and the intact side the left ( ) There was little increase in the maximum velocity of the slow phases when stimulating the ipsilateral ear nd more intense stimuli were unable to recruit faste slow phases *B Nystagmu induced by cold stimulation was of longer* duration from the ipsilateral (right) side than f m the contralateral side after lesion

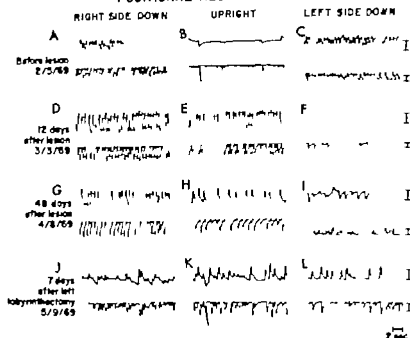


Fig. 24. Spontaneous alcohol nystagmus (upright) and positional alcohol nystagmus (right side down and left side down) before lesion (A–C), 12 and 48 days after lesion (D–I), and 7 days after contralateral labyrinthectomy (J–L). Note the strong spontaneous alcohol nystagmus to the right (ipsilateral side) after lesion (E). 48 days after lesion, however, it was possible to induce geotropic direction-changing PAN to both sides (G & I). After contralateral labyrinthectomy (J–L) there was no measurable effect of head position change on the spontaneous nystagmus after alcohol administration. The top trace in each pair is the horizontal EOG and the bottom trace shows slow phase velocity. The vertical bars are 20° for the EOG and 40°/sec for slow phase velocity.

nystagmus there was also strong directional preponderance of OKN and of caloric nystagmus to the right after left labyrinthectomy. However, it was still possible to induce contralateral and ipsilateral nystagmus by caloric stimulation of the ear on the lesion (right) side. Stronger (colder) caloric stimuli still failed to recruit slow phases of higher velocity as before lesion. OKAN could not be induced to the contralateral (left) side and was reduced in duration to the right.

Comment

The postural asymmetry and head tilt in 717 was more marked than in other monkeys including those with unilateral labyrinthectomy. After the initial contralateral nystagmus had subsided there was persistent directional preponderance of nystagmus to the ipsilateral side. This preponderance was not produced by unilateral labyrinthectomy or by root entry zone lesion as in 728 and was most likely a result of the rostral DVN lesion.

The major findings in this animal were that after lesion and contralateral labyrinthectomy, head position had no effect on the spontaneous nystagmus and PAN could not be induced. This did not occur after lesions of other parts of the vestibular nuclei. It seems likely that the rostral DVN lesion in 717 had caused an interruption of otolith-ocular reflex arcs from the ipsilateral ear. The lesion in 717 did not involve the most lateral portion of rostral DVN (Fig. 18 C, D), where the main inflow from the utricle enters the vestibular nuclei (Stein & Carpenter, 1967). We would

infer therefore that it was the destruction of the primary receiving area for this activity in rostral DVN rather than damage to the nerve root which was responsible for the findings in 717

Primary afferents which project into ventral LVN were destroyed in 717 and 728 This probably accounts for the changes in slow phase velocity and loss of recruitment on stimulation of the ipsilateral ear in both animals The larger difference in the slow phase velocities induced by cold than by hot stimuli in 717 (Fig. 23 A) than in 728 (Fig. 16 A) was probably due to the presence of ipsilateral directional preponderance in 717 The directional preponderance was probably responsible for the nystagmus of longer duration to the lesion side (right) than to the contralateral side (Fig 23 B) in 717

6 Lesion of Caudal Descending Vestibular Nucleus

Central and caudal parts of left DVN were destroyed in 712 (Fig. 25 C–E, 26). The rostral portion of DVN was intact (Fig. 25 A). There was slight involvement of caudal portions of MVN at the junction with DVN (Fig. 25 B–D). Gliosis and fiber loss was extensive throughout portions of DVN which had not been destroyed (Fig. 25 D, Fig. 26). The lesion did not involve the nerve roots and LVN. The restiform body was intact and the cerebellar nuclei were normal.

Stimulation through the implanted electrodes with pulse trains before the lesion caused ipsilateral (left) deviation of the eyes

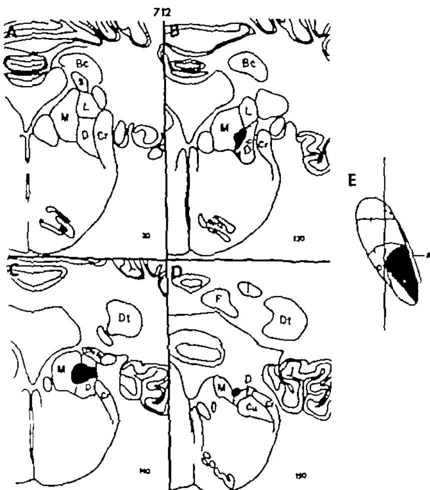


Fig. 25. A–D. Diagrams of lesion in Monkey 712. E. Extent of lesion in sagittal plane as seen from lateral aspect. The vertical line through E shows the plane of section for Figs. 25 A–D and 26. C. Cuneate nucleus.

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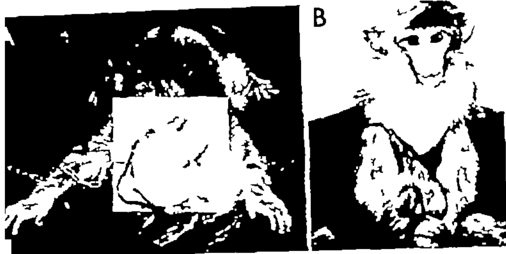


Fig 27 A, Strong falling tendency and head tilt to the left in 712 after left DVN lesion. B Head position and body posture after right labyrinthectomy

the left was present days after operation but it had disappeared when the animal was tested 5 days later

Head position continued to affect nystagmus after labyrinthectomy When the right (labyrinthectomy) side was down the spontaneous nystagmus to the left was enhanced When the left side was down the spontaneous nystagmus was inhibited

OKN tested 24 days after operation was almost symmetrical (Fig. 29 G H) The duration of OKAN was diminished bilaterally right more than left (Fig. 29 G H) Geotropic direction-changing PAN was induced to both sides after right labyrinthectomy (Fig. 30 J L). The total magnitude of the response 7 days after operation was about half that of the initial reaction.

Comment

The ipsilateral falling tendency and head tilt were striking in this animal The difficulty in maintaining upright posture would indicate that DVN has a strong effect on spinal motor systems. Postural imbalance was stronger after the caudal DVN lesion than after lesion of other parts of the vestibular complex. In particular there was a strong effect on the trunk which suggests that caudal DVN may have a close relation to lumbar and hindlimb muscles

Changes in caloric nystagmus and OKN were not striking after the caudal DVN lesion. The contralateral spontaneous nystag

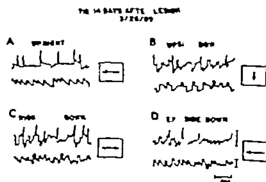


Fig 28 Spontaneous and positional nystagmus in Monkey 71... The vertical bars show 20° for the vertical (*upper trac*) and horizontal (*lower trac*) EOGs.

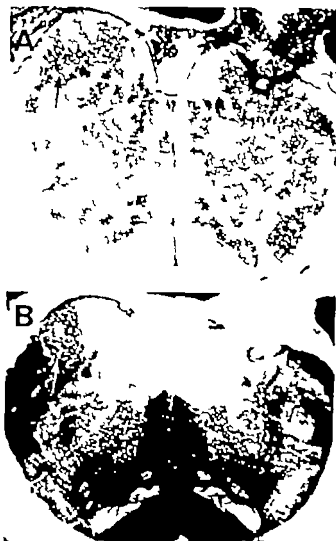


Fig 26 Cresyl violet (A) and Weil (B) stains showing the degeneration in DVN after lesion in 71 These sections were diagrammed in Fig. 25 D The atrophic DVN on the lesion (*left*) side can be compared to the normal DVN on the intact side (*arrow*).

with counterclockwise rotation (↶) Repetitive stimulation induced ipsilateral clockwise nystagmus (↷)

After lesion the animal hade severe dysequilibrium and was not able to sit upright for 4 days (Fig 27 A) The chin was rotated to the contralateral side and the occiput to the ipsilateral side The dysequilibrium was much more severe in 712 than in animals with unilateral labyrinthectomy (707 & 729) root entry zone lesion (728) or destruction of rostral DVN (717) Each of these animals was able to sit shortly after lesion

Spontaneous and positional nystagmus Spontaneous nystagmus was not present in this animal either in light or behind Frenzel glasses one day after lesion Later contralateral (right) spontaneous nystagmus was present in darkness (Fig 28 A) This was the only animal in whom apogeotropic direction changing positional nystagmus was prominent after the lesion When the right side was down the quick phases were directed to the left (Fig 28 C) and when the left side was down they were directed to the right (Fig 28 D) Upside down the nystagmus was downward (Fig 28 B) Both the spontaneous and positional nystagmus were still present when the animal was tested 30 days after lesion

OKN and OKAN OKN and OKAN were little affected by the DVN lesion (Fig 29 C–F) 3 days after lesion OKAN was of longer duration to the contralateral side (Fig 29 C) but was present to the ipsilateral side (Fig 29 D) It was more symmetric 10 days after lesion (Fig 29 E F)

Caloric nystagmus Caloric nystagmus also was not much affected by destruction of the central and caudal parts of DVN The nystagmus was somewhat stronger to the contralateral (right) than to the ipsilateral (left) side This was the direction of the spontaneous nystagmus (Fig 28 A)

PAN Despite the apogeotropic direction-changing positional nystagmus produced by the lesion geotropic direction-changing positional nystagmus was induced after administration of alcohol during PAN I (Fig 30 D F G I) The intensity of the nystagmus 6 days after DVN destruction (Fig 30 D F) was less than before lesion (Fig 30 A C) 29 days after lesion the intensity of PAN had recovered to pre-operative test levels (Fig 30 G I)

Right labyrinthectomy Labyrinthectomy was performed 70 days after the initial lesion After operation there was a slight head tilt to the right (Fig 27 B) There was no striking falling tendency to the right after labyrinthectomy Some spontaneous nystagmus to

mus in darkness may have been responsible for the slight contralateral directional pre ponderance of caloric nystagmus and OKN The findings suggest that caudal DVN is not much involved in processing information from the lateral semicircular canals

Apogeotropic direction-changing positional nystagmus was long lasting in this animal Similar positional nystagmus did not occur after lesions of other parts of the vestibular complex. This type of positional nystagmus has also been found after lesions of the cere bellar nuclei (Cohen et al 1969 Cohen & Highstein 1972) It is of interest in view of the close anatomical relationship between caudal DVN and the cerebellum (Brodal & Torvik, 1957 Carpenter 1960 Carpenter et al 1960 Angaut & Brodal 1967)

PAN I was induced 6 days after lesion (Fig. 30 D F) but was weaker than before lesion (Fig. 30 A C). The decrease in intensity may be explained by a subtraction of the apogeotropic direction-changing positional nystagmus due to the lesion from the geotropic PAN When the positional nystagmus decreased, the nystagmus of PAN I was stronger (Fig. 30 G I) PAN I was also in duced after contralateral labyrinthectomy (Fig. 30 K L) This suggests that the lesion had not directly affected portions of the vestibular nuclei which process the incoming in formation responsible for PAN This is in contrast to the loss of PAN after destruction of rostral DVN in 717 Caudal DVN probably maintains an indirect or secondary influence on information arising in the otolith organs

OPTOKINETIC STIMULATION 90 /sec 712

RIGHT OKN OKAN LEFT OKN OKAN

A Before lesion 2 7/69

B

C 3 days after lesion 3/14/69

D

E 10 days after lesion 3/2 /69

F

G 2 days after right labyrinthectomy 4/13/69

H

Fig 29 A–F OKN and OKAN before and after left DVN lesion and G H after contralateral (*right*) labyrinthectomy The top trace in each pair is a photocell recording showing passage of drum stripes The vertical bars show 70° for the horizontal EOG (*middle trace*) and 40°/sec for slow phase velocity (*bottom trace*)

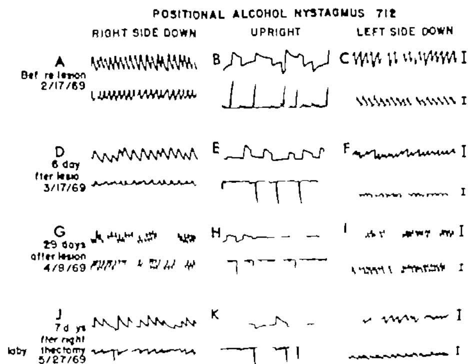


Fig 30 Positional alcohol nystagmus in 71 before (A C) and after (D F G I) left DVN lesion and after right labyrinthectomy (J L) Note that geotropi direction-changing PAN w pre sent after lesion (D F G I) and after right labyrinthectomy (J L) The ertical bars show 70° for the horizon tal EOG (*upper trac*) nd 40°/sec for the low phase elocity (*low er trac*)

mus in darkness may have been responsible for the slight contralateral directional preponderance of caloric nystagmus and OKN The findings suggest that caudal DVN is not much involved in processing information from the lateral semicircular canals

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7 Lesions of the Superior Vestibular Nucleus

724

Two animals (724 & 722) had lesions which destroyed the left SVN The lesion in 724 most closely approximated an isolated destruction of SVN Its findings will be contrasted to those in 722 and 727 which had lesions in and around SVN The extent of the destruction in 724 is shown in Figs 31 and 32 The lesion was confined to SVN and to ventral portions of the brachium conjunctivum About 3/4 of SVN was destroyed Only the rostral ventral portion of SVN was not directly damaged but it was gliotic and had few remaining neurons (Fig 31 A B 32 A B) The cerebellar nuclei were normal

Electrical stimulation through the implanted electrodes with pulse trains before lesion in 724 produced upward counterclockwise rotatory eye movements ( ) On repetitive stimulation nystagmus was induced with upward counterclockwise rotatory slow phases ( ) and downward clockwise rotatory



Fig 31 A F Diagram of lesion (black) and areas of demyelination and gliosis (stippled) in 724 G Sagittal view of vestibular nuclei from lateral aspect showing extent of destruction The vertical line through C shows the plane of section for A F and Figure 3

Fig. 32 Photomicrographs showing destruction and gliosis in 724. Cresyl violet stain. Section A corresponds to Fig. 31 A, B to Fig. 31 B, C to Fig. 31 C, and D to Fig. 31 E.

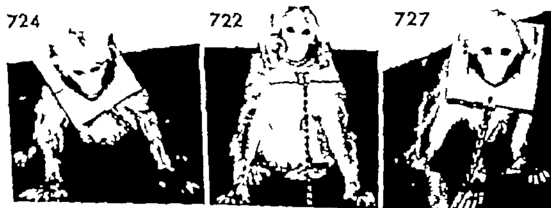


Fig. 33 Head position and body posture after lesion in 724, 722, and 727. Note the head tilt and falling tendency to the right in 724 and to the left in 727. 722 had little change in posture after lesion.

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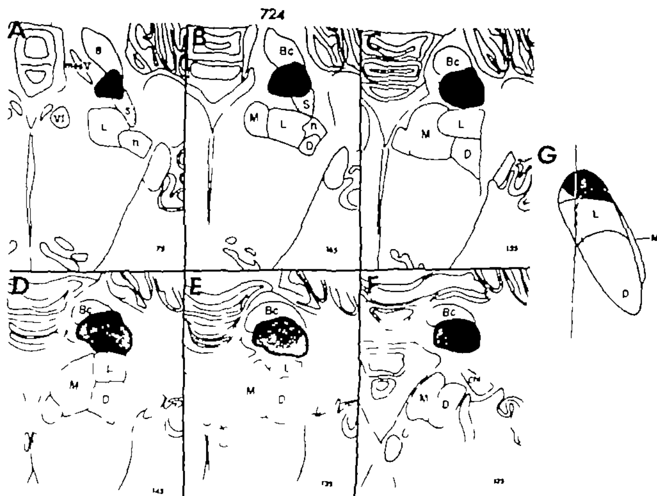


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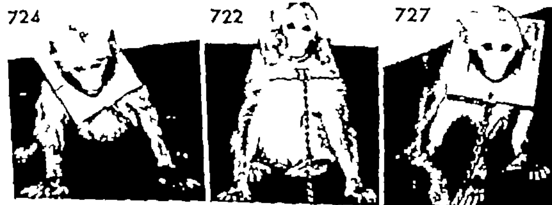


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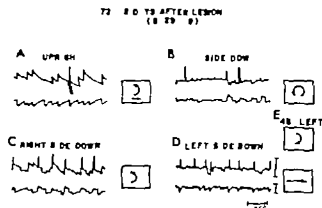


Fig 34 Spontaneous (A) and positional nystagmus (B–E) after lesion in 724 The vertical bars show 10° of deviation for the vertical *(upper trace)* and horizontal *(lower trace)* EOGs Only the direction of nystagmus is shown in E

quick phases ( ) After lesion there was a falling tendency to the opposite side in 724 (Fig 33) The monkey could sit upright but tended to support itself on all fours There was a slight head tilt to the contralateral (right) side

Spontaneous and positional nystagmus There was upward rotatory counterclockwise spontaneous nystagmus after the lesion (Fig 34 A) This nystagmus was just opposite in direction to that induced by repetitive electrical stimulation before lesion The spontaneous nystagmus lasted for 7 days in light and 10 days in darkness

Changes in head position induced striking positional nystagmus in 724 Two days after lesion when the contralateral (right) side was down the spontaneous upward counterclockwise rotatory nystagmus became weaker (Fig. 34 C) If the animal was tilted 45 toward the side of the lesion the nystagmus reversed and was downward clockwise rotatory in direction (Fig 34 E) With the ipsilateral (left) side down strong horizontal nystagmus was induced to the left without a significant rotatory component (Fig 34 D) Positional nystagmus with the left side down was horizontal for 7 days and then was mainly downward

OKN and OKAN OKN was induced to both sides after lesion in 724 There was preponderance of OKN to the ipsilateral side for the first two weeks (Fig 35 C D) The OKN was almost symmetrical 15 days after lesion (Fig 35 E F) OKAN was present to both sides after the SVN lesion although the duration of contralateral OKAN was shorter than

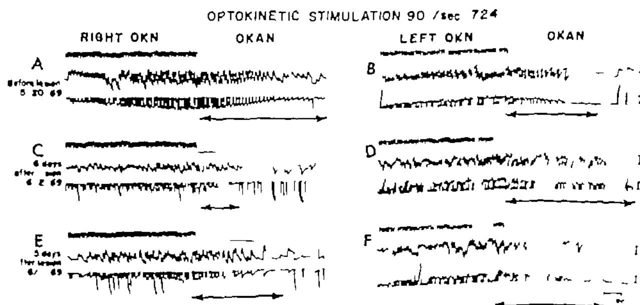


Fig 35 OKN and OKAN before (A B) and after (C–F) left SVN lesion in 724 The top trace in each pair is the photocell showing passage of drum stripes The vertical bars show 10° of deviation for the horizontal EOG (middle trace) and 40°/sec for the slow phase velocity (bottom trace)

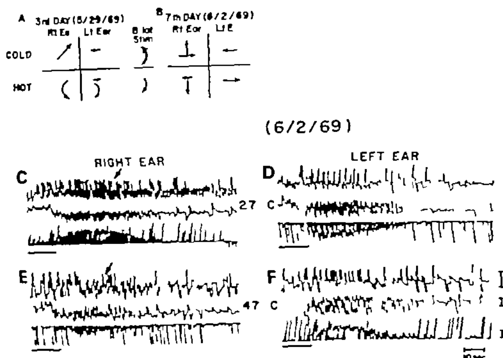


Fig. 36. Nystagmus induced by caloric stimulation in 724 3 and 7 days after left SVN lesion. The arrows in A, B show the direction of the nystagmus induced by caloric stimulation. B is diagrammatic representation of C–F. The top trace in C–F is the vertical EOG, the second trace the horizontal EOG and the third trace the slow phase velocity of the horizontal component of the nystagmus. The period of stimulation is shown by the underlying black bars. The vertical bars show 20° of deviation for the vertical and horizontal EOGs and 40°/sec for the horizontal slow phase velocity. The arrows in C and E point to the pronounced vertical component of the induced nystagmus.

that of ipsilateral OKAN on the 7th (Fig 35 C D) and 15 th day (Fig 35 E F) OKAN was more strongly affected after labyrinthectomy (707 & 779) or after lesions of the dorsal medullary reticular formation (734 see below)

Caloric nystagmus Perverted nystagmus was induced by caloric stimulation in 724 We define perverted caloric nystagmus as nystagmus induced by unilateral stimulation which is predominantly vertical instead of being horizontal or horizontal rotatory Results of testing 3 days after lesion are summarized in Fig 36 A. When the contralateral (right) ear was stimulated with cold water the nystagmus was oblique upwards and to the left. When the right ear was stimulated with hot water there was downward nystagmus with a counter clockwise rotatory component. When the ipsilateral (left) ear was stimulated with cold water the induced nystagmus was predominantly horizontal to the right However stimulation of the left ear with hot water also induced ipsilateral downward clockwise rotatory nystagmus

When both ears were simultaneously stimulated with cold water strong upward nystagmus was induced with some counterclockwise rotation (Fig. 36 A Bilat. Stim). Bilateral simultaneous stimulation with hot water produced weaker downward nystagmus which was clockwise

Perverted nystagmus was still induced at the end of the first week by stimulation of the

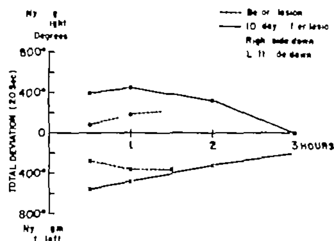


Fig 37 Graph of intensity of positional alcohol nystagmus before ( ) and after (—) lesion of left SVN in 724

contralateral ear with hot and cold water (Fig 36 B) This nystagmus is shown in Fig. 36 C–F The strong upward and downward components of the nystagmus induced by stimulation of the contralateral ear are indicated by the downward arrows over the vertical EOGs in Fig. 36 C and E (top traces) Only horizontal nystagmus was induced by stimulation of the ipsilateral ear (Fig 36 D F) There was some preponderance of the horizontal component of the nystagmus to the ipsilateral (left) side on both the 3rd and 7th day after lesion

Two weeks after lesion contralateral cold stimulation produced oblique upward nystagmus but the nystagmus caused by contralat

Fig 38 Diagrams of lesion in 722 A F are in the vertical stereotaxic plane and G is a diagram of the vestibular nuclei from the lateral aspect. The vertical line in G demonstrates the plane of section for A F and Figure 39

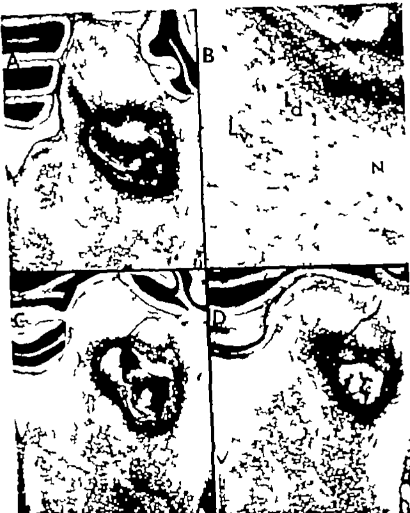


Fig. 39. Photomicrographs stained with cresyl violet of the lesion in 722. A and B correspond to Fig. 38 C, C to Fig. 38 D, and D to Fig. 38 E. *Lv* Ventral portion of LVN (small cell area). *Ld* Dorsal portion of LVN (giant cell area). V Vestibular nerve.

eral hot stimulation was now mainly horizontal. With the animal upside down, downward rotatory nystagmus was induced by stimulation of the contralateral ear with cold water. This was similar to that previously induced by stimulation with hot water with the animal upright (Fig. 36 A, B, Rt. Ear Hot).

PAN. Strong direction-changing positional nystagmus was induced during PAN I 10 days after lesion (Fig. 37, solid lines). This nystagmus was more intense than before operation (dotted lines). Strong downward nystagmus was present during PAN I with the animal upright, and upward nystagmus was present when the animal was upside down.

16 days after lesion, the monkey developed continuous seizures caused by metal screws in the skull cap and was sacrificed. Contralateral labyrinthectomy was not performed.

722

The lesion was more extensive in 722 than in 7'4. It entirely destroyed SVN (Fig. 38 A–D, G). It also damaged ventral parts of the brachium conjunctivum (Fig. 38 C–E, 39 A, C), dorsal portions of LVN (Fig. 38 B–D, 39 A, B) and slightly impinged on the dorsal part of the vestibular nerve (Fig. 38 D). Figure 39 B is a higher magnification of the partial destruction of dorsal LVN (Ld). Brachium

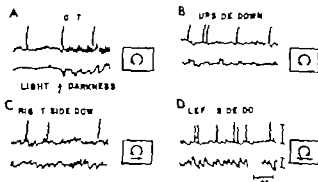


Fig 40 Spontaneous (A) and positional nystagmus (B–D) after lesion in 722 The vertical bars represent 20° for the vertical EOG (*upper trace*) and horizontal EOG (*lower trace*)

conjunctivum destruction was less in 722 than in 724 The cerebellar nuclei were normal

Aside from a slight ipsilateral head tilt and falling tendency there was little change in posture in 722 (Fig 33) This was in contrast to the more striking postural effects of the SVN lesion in 724 Stimulation through the implanted electrodes with pulse trains prior to the lesion induced ipsilateral oblique (left) eye movements (↗) With repetitive stimulation ipsilateral horizontal clockwise rotatory nystagmus was induced (↷)

Spontaneous and Positional Nystagmus After lesion the spontaneous nystagmus was counterclockwise rotatory (Fig 40 A) with a strong upward component (top trace Fig 40 A) The upward component was similar to that found in 724 (compare top traces in Figs 34 A and 40 A) Spontaneous nystagmus was present in light for about 8 days and in darkness for about 1 month

Positional nystagmus was striking in two ways in 722 (1) It was almost entirely in the coronal plane (2) The rotatory component of the nystagmus reversed direction when the animal s head position was reversed When the ipsilateral (left) side was down there was clockwise nystagmus (Fig 40 D) When the contralateral (right) side was down the nystagmus was rotatory and counterclockwise (Fig 40 C) This direction-changing rotatory positional nystagmus persisted until the animal s death 31 days after lesion A similar reversal of rotatory nystagmus due to change in head position was also present in 724 (Fig 34 A E)

OKN and OKAN There was initially a slight preponderance of OKN to the ipsilateral (left) side OKAN was present but it was initially somewhat shorter to the contralateral than to the ipsilateral side

Caloric Nystagmus On the 3rd day there was a slight directional preponderance of caloric nystagmus to the ipsilateral side The nystagmus induced by stimulation of the opposite ear with cold water or of the ear on the lesion side with hot water was accompanied

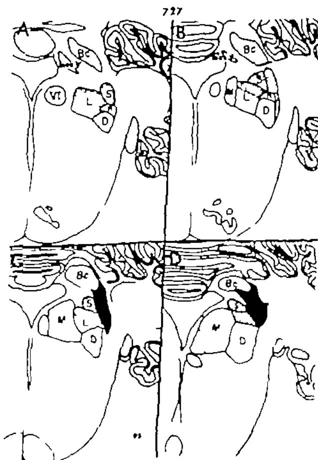


Fig 41 Diagrams of the destruction (black) and demyelination and gliosis (stippled) in 727 mes 1 Mesencephalic trigeminal nucleus VI Abducens nucleus

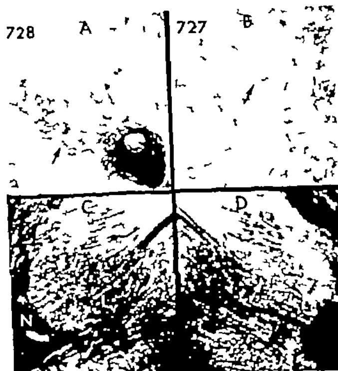


Fig 42 A. Gliosis in ventral LVN after nerve root lesion in 728 See also Figures 11 & 1 which show xtent of lesion in this animal. B gliosi and, D demyelination in dorsal LVN after destruction of the brachium conjunctivum and restiform body in 727 The normal LVN and vestibular nerve on the intact side are shown in C. A. B cresyl violet and C, D Weil stains.

by an upward component The animal had a strong upward component to the spontaneous nystagmus at that time On the 8th and 16th days the nystagmus induced by hot and cold stimulation was mainly horizontal and was symmetrical

722 developed seizures presumably due to metal screws in the skull cap after 1 month and did not have a contralateral labyrinth ectomy

727

This animal had a lesion in ventro-lateral parts of the brachium conjunctivum and the medial part of the restiform body (Figs. 41 C D) There was gliosis and a loss of fibers in SVN and in dorsal LVN (Fig 41) showing that much of the afferent cerebellar input to these nuclei had been interrupted There was little direct damage to SVN and ventral LVN was intact. The gliotic demyelinated dorsal LVN in 727 (Fig 4 B D arrows) can be contrasted to the normal LVN on the opposite side (Fig. 4 C) Differences in ventral LVN due to nerve root lesion in 728 and in dorsal LVN due to a brachium conjunctivum and restiform body lesion in 727 are shown in Fig 42 A B

Stimulation through the electrodes with pulse trains or repetitive stimulation prior to the lesion in 727 caused strong ipsilateral horizontal eye deviations (→) but not nystagmus After lesion there was a falling tendency to the ipsilateral side (Fig. 33)

Spontaneous and positional nystagmus Spontaneous nystagmus was not striking in 727 There was some ipsilateral counter clockwise rotatory nystagmus just after lesion (◡) and contralateral nystagmus 8 days after lesion.

Head position had some effect on the spontaneous nystagmus in this animal. As in 722 the rotatory nystagmus *was intensified when the contralateral side was down. However there was no reversal of the rotatory nystagmus when the ipsilateral side was down as in 72_ or in 724*

OKN and OKAN 8 days after lesion

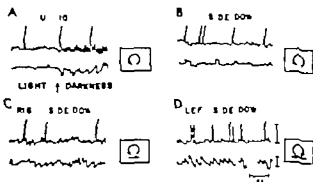


Fig 40 Spontaneous (A) and positional nystagmus (B–D) *after lesion in 722. The vertical bars represent* 10° for the vertical EOG (*upper trace*) and horizontal EOG (*lower trace*).

conjunctivum destruction was less in 722 than in 724 The cerebellar nuclei were normal

Aside from a slight ipsilateral head tilt and falling tendency there was little change in posture in 722 (Fig 33) This was in contrast to the more striking postural effects of the SVN lesion in 724 Stimulation through the implanted electrodes with pulse trains prior *to the lesion induced ipsilateral oblique (left) eye movements (   ) With repetitive stimulation ipsilateral horizontal* clockwise rotatory nystagmus was induced (↷)

Spontaneous and Positional Nystagmus After lesion the spontaneous nystagmus was counterclockwise rotatory (Fig 40 A) with *a strong upward component (top trace Fig* 40 A) The upward component was similar to that found in 724 (compare top traces in Figs 34 A and 40 A) Spontaneous nystagmus was present *in light for about 8 days* and in darkness for about 1 month

Positional nystagmus was striking in two ways in 722 (1) It was almost entirely in the coronal plane (2) The rotatory component of the nystagmus reversed direction when *the animal's head position* was reversed When the ipsilateral (left) side was down there was clockwise nystagmus (Fig 40 D) When the contralateral (right) side was down the nystagmus was rotatory and counterclockwise (Fig 40 C) This direction-changing rotatory positional nystagmus persisted until the animal's death 31 days after lesion A *similar reversal of rotatory nystagmus due to* change in head position was also present in 724 (Fig 34 A E)

OKN and OKAN There was initially a slight preponderance of OKN to the ipsilateral (left) side OKAN was present but it was initially somewhat shorter to the contra*lateral than to the ipsilateral side*

Caloric Nystagmus On the 3rd day there was a slight directional preponderance of caloric nystagmus to the ipsilateral side The nystagmus induced by stimulation of the opposite ear with cold water or of the ear on the lesion side with hot water was accompanie

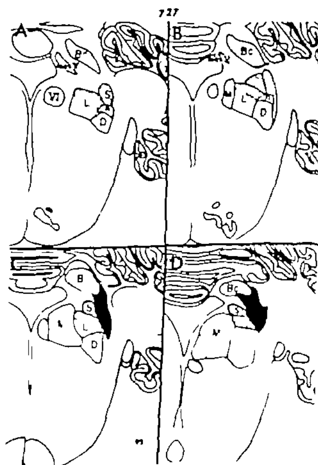


*Fig 41 Diagrams of the destruction (black) and de*myelination and gliosis (stippled) in 722 M Mesencephalic trigeminal nucleus VI Abducens nucleus

in view of the inhibitory nature of the cerebello-vestibular pathways from the flocculus (Ito et al 1970 Baker et al 1972 Fukuda et al. 1977) One possibility is that interruption of these pathways may have resulted in some dysinhibition of otolith-ocular reflexes. This is consistent with the finding that PAN was enhanced after the lesion in 724 and that active downward nystagmus appeared in the upright position during PAN I There are no (Gacek, 1969) or few (Stein & Carpenter 1967) direct afferent projections from the otolith organs to SVN so that presumably the positional nystagmus is related to activity mediated through the cerebellum

The horizontal component of caloric nystagmus was preserved in 722 and 724 although SVN was partially or completely destroyed The main effect of the SVN lesions on horizontal nystagmus was to cause some ipsilateral directional preponderance If a primary area for production of horizontal caloric nystagmus were destroyed one would expect contralateral directional preponderance and spontaneous nystagmus as after labyrinthectomy (707 729). It can be concluded that SVN is not an essential nucleus for production of horizontal nystagmus induced by the lateral semicircular canal

The main effect of the SVN lesions on caloric nystagmus was an enhancement of vertical components particularly when induced by stimulation of the ear on the *contralateral* (right) side According to arguments given in the Methods Section a unilateral caloric stimulus simultaneously excites both the lateral and anterior semicircular canals although horizontal nystagmus from the lateral canal predominates in the observed response The accentuation of vertical caloric responses on right-sided stimulation seemed most likely to be due to an enhancement of nystagmus induced by the right anterior canal. Nystagmus with similar vertical and rotatory components would be induced by excitation or inhibition of the right anterior canal but could not be produced by the right posterior canal (Fig. 3 D E) Speculative explanations for the enhancement or dysinhibition of the anterior canal responses will be considered in the General Discussion

there was some preponderance of OKN to the right which agreed with the direction of the spontaneous nystagmus OKAN was reduced to the ipsilateral side

Caloric nystagmus Three days after lesion caloric nystagmus was stronger when quick phases were to the ipsilateral side Later the spontaneous nystagmus reversed and caloric nystagmus was stronger when it was to the opposite side 3 days after lesion an upward component was present when the ipsilateral ear was stimulated with hot or the contralateral ear with cold water When both ears were simultaneously stimulated with cold water on the 8th day strong upward nystag mus was induced No downward nystagmus was induced by bilateral hot stimulation at that time

Comment

Two major projection systems end in SVN They come from the ipsilateral semicircular canals (Stein & Carpenter 1967 Gacek 1969) and from the cerebellum (Walberg et al 1962 Angaut & Brodal 1967) 724 had a fall ing tendency to the contralateral side spon taneous nystagmus with a definite ipsilateral component and ipsilateral directional prepon derance of OKN and caloric nystagmus None of these findings occur after unilateral laby rinthectomy Therefore the findings in 724 could not be attributed solely to a reduction of afferent inflow from the ipsilateral semi circular canals

Similarly body postural changes were differ ent in 724 after SVN destruction than in 727 after a lesion of cerebello-vestibular path ways 727 had a strong falling tendency to the ipsilateral side while in 724 the falling tend ency was to the contralateral side Thus the postural changes in 724 were not due to damage of cerebello-vestibular pathways Rather the postural changes appeared to be due to intrinsic damage to SVN itself Another monkey (453) had more extensive destruction of the brachium conjunctivum but also did not have similar postural changes or spontaneous nystagmus as 724 McMasters et al (1966) also noted that monkeys with SVN lesions tended to develop head tilt toward the opposite shoulder

Postural changes in 724 and 722 (Fig 33) are the reverse of what might be expected from the size of the lesions The lesion in 722 was the largest of any in the series yet the postural changes were less than in 724 A speculative explanation for this is that there was a summation of postural changes produced by lesions of several different struc tures That is contralateral head and body tilt due to SVN destruction (Fig 33 724) may have added the ipsilateral head and body tilt due to LVN or vestibular nerve lesions (Fig 13 A) or restiform body lesions (Fig 33 727) to produce the relatively minor overt effect on body posture in 722 Postural effects were tested only by observing the ani mals sitting and walking just after lesion and more subtle changes would be missed

The direction of the spontaneous nystagmus after lesion in 724 was just the reverse of the nystagmus induced by stimulation It would appear that the left SVN lesion had caused a change in eye movements in spatial planes represented by the left anterior or right posterior canal (Fig 3 D E also Suzuki et al 1964 Suzuki & Cohen 1964 Cohen et al 1966) Nystagmus with these rotatory and vertical components would not be induced either by excitation or destruction of the left posterior or right anterior canals (Fig 3 D E)

There was positional nystagmus in each of the animals with lesions of SVN (722 724) or of afferent pathways to SVN (727) It was counterclockwise when the right side was down in all 3 monkeys (Fig 34 C 40 C) and clockwise when the left side was down in 722 (Fig 40 D) or when the head was 45° to the left in 724 (Fig 34 E) There was no clockwise nystagmus when the ipsi lateral side was down in 727 The prominent positional nystagmus with the contralateral side down in all three animals is of interest



Fig 44 Photomicrographs through the center of the lesions in 588 715 700 and 701 Cresyl violet stain.

However in 701 the lesion extended laterally and there was some involvement of SVN and LVN (Fig 43 D stippled area) In 73? the lesion was much larger than in the other MVN animals Central parts of MVN were destroyed at the junction with DVN (Fig 45 A B) but rostral MVN was intact (Fig. 45 A Inset 45 B)

Postural effects of the MVN lesions were minimal There was no head tilt or falling tendency in monkeys with lesions of rostral MVN (588 700 701) or central MVN (73) Fig. 46 A) In 715 there was a slight head tilt and falling tendency to the contralateral side (Fig. 46 B).

Spontaneous and positional nystagmus Spontaneous nystagmus was not prominent in these animals It was present for not more than ? days in light and 5 days in darkness in all but 701 In that animal it was present until the 13th day The spontaneous nystagmus was contralateral in 588 and 732 and ipsilateral in 700 701 and 715

Positional nystagmus was also not prominent in 4 of the 5 animals after MVN lesions In 701 geotropic direction-changing positional nystagmus was induced with some upward vertical component in the EOG

OKN and OKAN Changes in OKN were relatively minor after MVN lesions and

8 Lesions of the Medial Vestibular Nucleus

Five animals had lesions of the left MVN 588 700 701 715 and 732. In 588 the destruction was confined to rostral MVN It was about 1 mm wide and extended about 1 5 mm in rostro-caudal direction (Fig 43 A) The lesion was surrounded by a zone of gliosis which extended through rostral MVN (Fig 44 A) Neither the central nor caudal portions of MVN nor the other vestibular nuclei were affected in 588 In 715 the lesion destroyed the lateral dorsal part of rostral MVN and part of the adjacent LVN (Fig. 43 B 44 B) The lesion was more lateral and dorsal than in 588 In 700 and 701 the lesions were about 1 mm in diameter and were almost identical destroying the rostrodorsal portions of left MVN at the junction with the fourth ventricle (Fig 43 C D 44 C D)

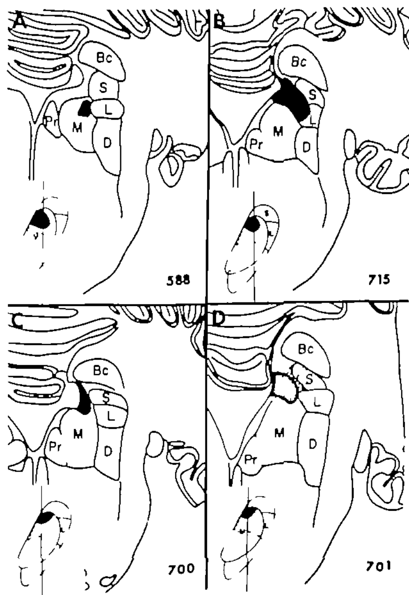


Fig 43 Diagrams of lesion (black) and areas of demyelination and gliosis (stippled) in 588 715 700 and 701 The insets show the extent of the lesions in sagittal drawings of the vestibular nuclei seen from the medial aspect The vertical lines show the plane of section in Figures 43 & 44

Fig 47 Diagrammatic representation of nystagmus induced by hot and cold caloric stimulation in Monkeys 588 (A–D) 700 701 and 715 (E–H) and 774 (I–L) The direction of quick phases of nystagmus in the normal caloric reaction is shown in M–P Note that stimulation of the contralateral (*right*) ear with cold water induced upward oblique nystagmus and hot water downward counterclock wise rotatory nystagmus after either the left MVN or SVN lesions

to the contralateral side in 700 701 and 715 and to the ipsilateral side in 588

Caloric nystagmus Caloric nystagmus was affected in a characteristic way by lesions of the rostral portion of MVN The nystagmus is represented diagrammatically in Fig 47 and examples of EOGs are shown in Fig. 48 for 588 and 700 Findings in 701 and 715 were similar to those in 700 Vertical components are shown in the top traces of Fig 48 and horizontal components in the 2nd and 3rd traces. These record the vertical EOG the horizontal EOG and the horizontal slow phase velocity respectively

When the ear on the side *contralateral* to the lesion (right) was stimulated the induced nystagmus was predominantly vertical With hot water downward counterclock wise nystagmus was induced (Fig. 47 C G) There was little or no horizontal component in the nystagmus (Fig 48 C G middle and bottom traces) When the right ear was stimulated with cold water the induced nystagmus was oblique upward (Fig 47 A E) The horizontal component of this nystagmus was preserved (Fig. 48 A E middle and bottom traces) Changes in vertical components of nystagmus induced from the contra lateral ear were long-lasting in 588 (more than 3 months) and were of shorter duration in 700 701 and 715 (about 1 month) Later contralateral cold stimulation induced predominantly horizontal nystagmus in these animals

When the ear ipsilateral to the lesion side (left) was stimulated with cold water the induced nystagmus was horizontal in all 4 animals (Fig 47 B F 48 B F) Stimulation of the left ear with hot water provoked down ward clockwise nystagmus in 588 for more than 3 months (Fig. 47 D 48 D) In 700 701 and 715 only horizontal nystagmus was induced by ipsilateral hot stimulation (Fig 47 H 48 H)

588 was tested when upside down The response to stimulation with hot and cold water was the reverse of the patterns shown in Fig 47 A–D Double simultaneous hot and cold stimulation in 588 in the upright position produced active downward and upward vertical nystagmus in the midsagittal plane respectively

PAN PAN was not affected in any of the animals with MVN lesions Geotropic direction-changing PAN in 715 which was some what more active after than before lesion is shown in Fig 49 B

Labyrinthectomy 715 had a right labyrinthectomy After operation there was a strong head tilt and falling tendency to the right (Fig 46 C) Spontaneous nystagmus was present to the left It persisted in darkness until sacrifice 4? days later This nystagmus was increased when the side of the labyrinthectomy was down and decreased when the contralateral side was down There was directional preponderance of OKN in the same direction as the spontaneous nystagmus OKAN was induced after right labyrinthectomy but was of short duration, ipsilateral less than contralateral

Nystagmus to the right and left was induced

Fig 45 A Diagrams and B photomicrograph through the center of the lesion in 732 The inset in A is a sagittal view of the vestibular nuclei from the medial aspect showing the extent of destruction and the plane of section.

agreed with the direction of the spontaneous nystagmus In 700 701 and 715 there was ipsilateral preponderance of OKN for about 1 week In 588 the OKN preponderance was to the contralateral side OKN was not tested in 732 Changes in OKAN were also relatively minor and mirrored the spontaneous nystagmus The duration of OKAN was decreased

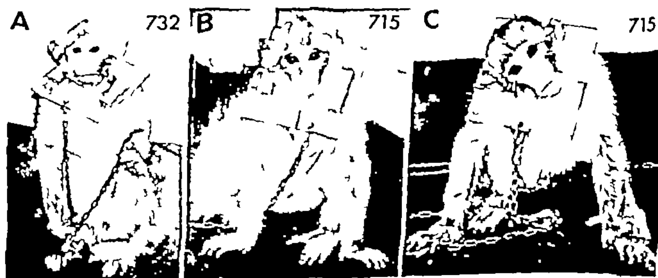


Fig 46 Head position and body posture in 732 (A) after a central MVN lesion and (B) in 715 after a rostral MVN lesion Effect of subsequent right labyrinthectomy in 715 are shown in C

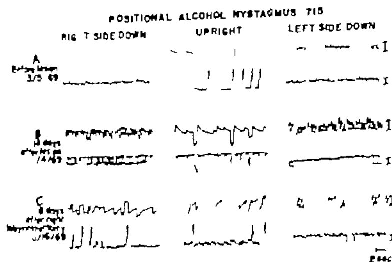


Fig. 49 EOGs showing spontaneous and positional alcohol nystagmus before (A), after (B) left MVN lesion in 715. Effects of right labyrinthectomy are shown in C. The vertical bars show 30° of deviation for the horizontal EOG (*upper trace*) and 60°/sec for the slow phase velocity (*bottom trace*).

the descending projections from rostral and central MVN was not elucidated by this study.

Spontaneous nystagmus was ipsilateral in 3 of 5 monkeys (700, 701 and 715) and transiently contralateral in the other two animals (588, 732). Similarly, nystagmus was ipsilateral after SVN destruction.

Positional nystagmus was not present in 588, 700, 715 and 732. Moreover, PAN was not abolished by the MVN lesion after contralateral labyrinthectomy in 715. Although there was some positional nystagmus in 701, it seems likely that it was due to involvement of adjacent parts of SVN. Rostral MVN does not appear to be a critical area for processing information which originates in the otolith organs.

The horizontal component of caloric nystagmus induced by stimulation of either ear with cold water was preserved in each of the animals after rostral and central MVN lesions. These findings indicate that portions of rostral and central MVN which were destroyed were not critical for production of horizontal nystagmus induced by the lateral semicircular canals. The weak spontaneous nystagmus after MVN lesions is in accord with this conclusion. Spontaneous nystagmus was much stronger after unilateral labyrinthectomy (707, 729) or after root entry zone destruction (728).

Perverted nystagmus with enhanced vertical components induced by stimulation of the contralateral ear was similar in animals with MVN (Fig. 47 A, C, E, G) and SVN lesions (Fig. 47 I, K). The perverted nystagmus persisted for a longer time after the MVN lesion in 588 and in addition persistent perverted nys-

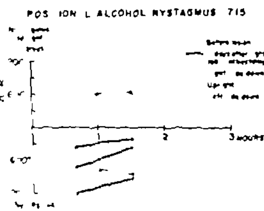
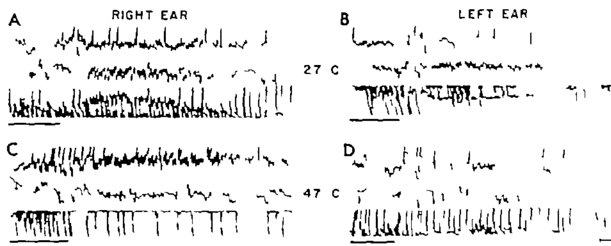


Fig. 50. Graph of intensity of nystagmus during PAN before ( ) and after left MVN lesion and contralateral (*right*) labyrinthectomy (——) in 715. The strong spontaneous nystagmus (●—●) after the left MVN lesion and right labyrinthectomy was enhanced in the left-side down position (—) and reduced in the right-side down position (○—○).



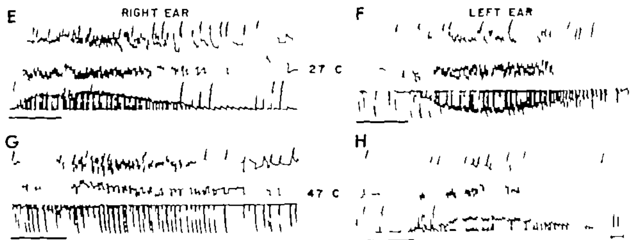


Fig 48 Caloric nystagmus in 588 (A D) and 700 (E–H) after left MVN lesions The nystagmus is represented diagrammatically in A–H of Figure 47 The top trace is the vertical EOG The second trace is the horizontal EOG and the lower trace records horizontal slow phase velocity Note the strong upward and downward nystagmus in the vertical EOG (top trace of A C E & G) when the contralateral (*right*) ear was stimulated with cold or hot water The horizontal component of the response to stimulation of the right ear [illegible] hot water (2nd and 3rd traces of C & G) was [illegible] markedly diminished The vertical bars show [illegible] deviation for the vertical and horizontal EOG and 50°/sec for horizontal slow phase velocity (bottom trace)

by hot and cold stimulation of the left ear respectively after contralateral labyrinthectomy

Alcohol administration 8 days after labyrinthectomy caused a diminution of slow phase velocity of the spontaneous nystagmus when the labyrinthectomy side (right) was down and an increase in slow phase velocity when the contralateral side was down (Fig 49 C 50 solid lines)

Comment

Postural changes were not striking after lesions in any of the animals after MVN lesions 715 had a slight contralateral head tilt but it was minimal Neurons in MVN send axons to the spinal cord via the MLF The spinal projection of MVN is much smaller than its ascending projection (Wilson et al 1968 a) or than the vestibulospinal projection from LVN (Nyberg Hansen 1964) The function of

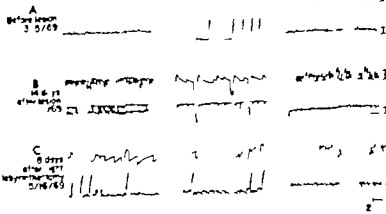


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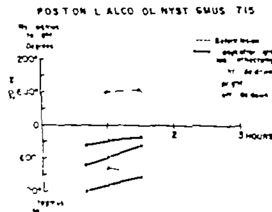


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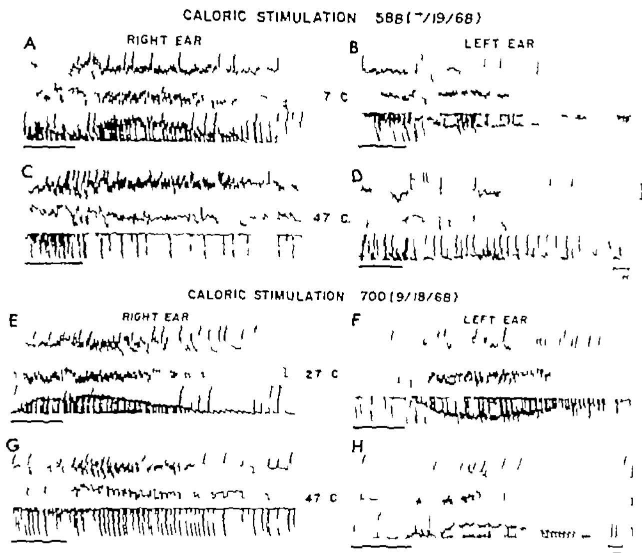


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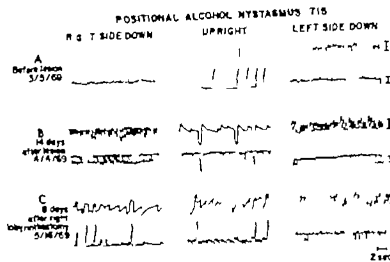


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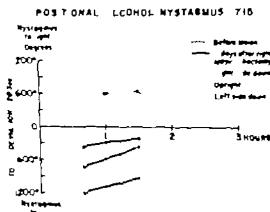
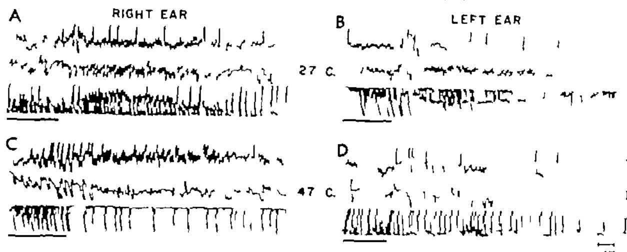


Fig 50 Graph of intensity of nystagmus during PAN before ( ) and after left MVN lesion and contralateral (right) labyrinthectomy (——) in 715. The strong spontaneous nystagmus ([illegible]) after the left MVN lesion and right labyrinthectomy was enhanced in the left-side down position (—) and reduced in the right-side down position (O—O).

4-[illegible]



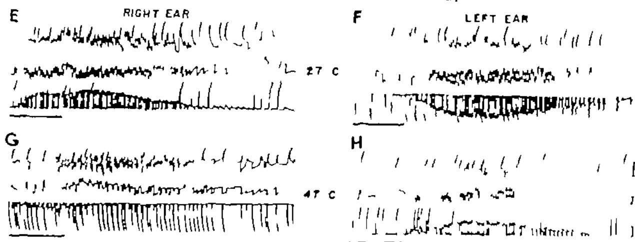


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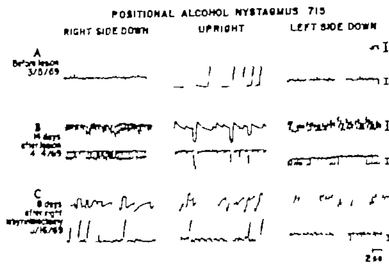


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Spontaneous nystagmus was ipsilateral in 3 of 5 monkeys (700 701 and 715) and transiently contralateral in the other two animals (588 732). Similarly nystagmus was ipsilateral after SVN destruction

Positional nystagmus was not present in 588 700 715 and 732. Morever PAN was not abolished by the MVN lesion after contralateral labyrinthectomy in 715 Although there was some positional nystagmus in 701 it seems likely that it was due to involvement of adjacent parts of SVN Rostral MVN does not appear to be a critical area for processing information which originates in the otolith organs

The horizontal component of caloric nystagmus induced by stimulation of either ear with cold water was preserved in each of the animals after rostral and central MVN lesions These findings indicate that portions of rostral and central MVN which were destroyed were not critical for production of horizontal nystagmus induced by the lateral semicircular canals The weak spontaneous nystagmus after MVN lesions is in accord with this conclusion Spontaneous nystagmus was much stronger after unilateral labyrinthectomy (707 7?9) or after root entry zone destruction (728)

Perverted nystagmus with enhanced vertical components induced by stimulation of the contralateral ear was similar in animals with MVN (Fig. 47 A C E G) and SVN lesions (Fig. 47 I K). The perverted nystagmus persisted for a longer time after the MVN lesion in 588 and in addition persistent perverted nys

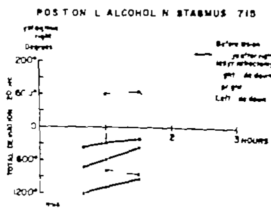


Fig 50 Graph of intensity of nystagmus during PAN before ( ) and after left MVN lesion and contralateral (*right*) labyrinthectomy (——) in 715 The strong spontaneous nystagmus (●—●) after the left MVN lesion and right labyrinthectomy was enhanced in the left-side down position (—) and reduced in the right-side down position (○—○)

tagmus was induced by ipsilateral hot stimulation (Fig 47 D) This suggests that the perversion after MVN lesions was not only due to loss of activity which originated in SVN but to an intrinsic effect of MVN on the perverted responses as well After both MVN and SVN lesions the vertical responses were more striking and were induced for longer periods of time with hot than with cold stimuli with the animals upright The reverse was true with the animals upside down This indicates that perversion was greater when there was an increase rather than a decrease in acitivity in the primary afferent vestibular nerve fibers

9 Lesions Medial to the MVN

Two monkeys 586 and 734 had lesions just medial to left MVN These lesions involved the dorsal medullary reticular formation and the prepositus hypoglossi between MVN and the MLF (Figs 51 & 52 A & B) In 586 the lesion began just behind the abducens nucleus and lay medial to MVN in its central portion (Fig. 51 A) In 734 the lesion was larger It began at the caudal lateral end of the abducens nucleus, and was located in the dorsal medullary reticular formation and the medial portion of central MVN (Fig. 52 B) There was some gliosis and cell loss in the most medial portions of MVN in both animals.

The findings in these animals were similar The animals had a strong head tilt and a falling tendency to the ipsilateral side (Fig 53 A) The head tilt was stronger in 734 than in 586 and persisted for one month until right labyrinthectomy

Spontaneous gaze and positional nystagmus Both monkeys initially had gaze nystagmus on either right or left lateral gaze Gaze nystagmus persisted on looking to the ipsilateral (left) side for more than 1 month There was also ipsilateral spontaneous nystagmus in darkness in both animals during the period of observation Geotropic direction-changing positional nystagmus was present in 586 for 3 months In 734 the spontaneous nystagmus to the ipsilateral side had a tendency to increase when the contralateral side was down

OKN There was strong directional preponderance of OKN to the ipsilateral (left) side in both animals after lesion The left directional preponderance persisted in 734 until right labyrinthectomy 29 days later (Fig. 54 B C) In 586 it was present for more than 2 months OKAN was lost after the medullary reticular formation lesion in both of these animals. It was absent at the time of right labyrinthectomy in 734 (Fig. 54 C) Some OKAN was present on the 38th day in 586 (Lt>Rt)

Caloric nystagmus The direction of caloric nystagmus was not changed by lesions in 586 and 734 There was directional pre

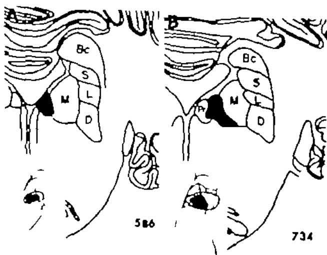


Fig 51 Diagrams of the lesions in 586 and 734 The insets show the lesions placed against the vestibular nuclei as seen from the medial aspect. The circles show the extent of lesion and the black areas, the regions where the lesion affected the adjacent parts of MVN The vertical lines show the plane of section.



Fig 52 Photomicrographs from 586 (A) and 734 (B) of the sections shown in Figure 51

ponderance to the ipsilateral (left) side (Figs 55 & 56 A) but it was not as strong as the directional preponderance of OKN (Fig 54 B) and disappeared within a month The left directional preponderance was not reflected in differences in nystagmus duration in 734 (Fig 56 B) Bilateral cold and hot stimulation induced upward and downward nystagmus respectively after the lesion in 586

PAN PAN was unaffected by the lesions in these animals

Labyrinthectomy 734 had a right labyrinthectomy 29 days after lesion Before operation there was still a slight head tilt to the ipsilateral (left) side at the time of operation Following operation the head tilt disappeared (Fig 53 B) There was no falling tendency Spontaneous nystagmus was present to the left in light and in darkness for 1 month until sacrifice Associated with the spontaneous nystagmus to the left there was also strong directional preponderance of OKN to the left There was no OKAN in either direction after labyrinthectomy (Fig. 54 D)

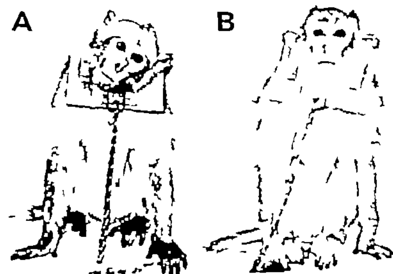


Fig 53 Head position and body posture in 734 after left dorsal medullary reticular formation lesion (A) and right labyrinthectomy (B)

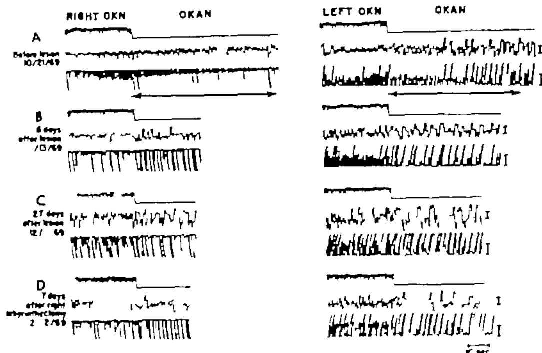


Fig 54 Optokinetic nystagmus and after-nystagmus in 734 before lesion (A), 6 and 27 days after lesion (B C) and after right labyrinthectomy (D). Note the absence of OKAN 6 and 77 days after lesion and after right labyrinthectomy The vertical bars show 22° for the horizontal EOG (second trace) and 45°/sec for the slow phase velocity (third trace).

Caloric nystagmus was induced to either side after labyrinthectomy It reflected the directional preponderance to the left That is the response to the left induced by hot water was stronger than that to the right induced by cold water

PAN was present to the right and to the left 1 and 25 days after lesion

Comment

There were a number of differences between animals with dorsal medullary reticular formation lesions (734 and 586) and animals which have been described previously (1) There was a strong ipsilateral head tilt in 586 and 734 In animals with lesions of the adjacent rostral or central MVN the head tilt was to the contralateral side or was not striking (2) The direction of head tilt after the lesion in 586 and 734 was the same as the direction of the quick phases of the spontaneous nystagmus. This is in contrast to monkeys with lesions inside the vestibular nuclei. In these animals the head tilt and falling tendency were to the same side as the slow phases of the spontaneous nystagmus.

(3) Gaze nystagmus was present for more than one month in both 586 and 734 Gaze nystagmus was not found after lesions of the vestibular nuclei (4) Changes in OKN were striking and of long duration and OKAN was abolished for considerable periods or was lost in these animals Neither OKN nor OKAN was similarly affected in any animals with vestibular nuclei lesions (5) Caloric nystagmus and PAN were not as severely



Fig 52 Photomicrographs from 586 (A) and 734 (B) of the sections shown in Figure 51

ponderance to the ipsilateral (left) side (Figs 55 & 56 A) but it was not as strong as the directional preponderance of OKN (Fig 54 B) and disappeared within a month The left directional preponderance was not reflected in differences in nystagmus duration in 734 (Fig 56 B) Bilateral cold and hot stimulation induced upward and downward nystagmus respectively after the lesion in 586

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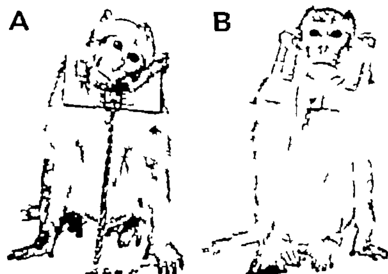


Fig 53 Head position and body posture in 734 after left dorsal medullary reticular formation lesion (A) and right labyrinthectomy (B).

present after lesions of the dorsal medullary reticular formation.

There is no clear explanation for the long lasting positional nystagmus in 586 734 with a larger lesion in the same area did not have positional nystagmus Despite the close proximity of MVN and the dorsal medullary reticular formation the differences in oculomotor and postural changes after lesions show that these regions must function quite separately

CALORIC STIMULATION 734 (11/13/69)

RIGHT EAR | LEFT EAR

17 C

27° C

32 C

35 C

47 C

10 sec

Fig 55 Nystagmus induced by stimulation of the right and left ears with different water temperatures in 734 The top trace is the horizontal EOG the second trace is slow phase velocity and the bar under the slow phase velocity trace shows the duration of stimulation The vertical bars are 22° for the horizontal EOG and 45°/sec for the slow phase velocity

affected as OKN by the dorsal medullary reticular formation lesions Therefore it seems likely that the damage was not in primary pathways which carry information from the semicircular canals or otolith organs to the eye muscle motor nuclei Enhanced vertical components of caloric nystagmus i e perverted caloric responses were also not

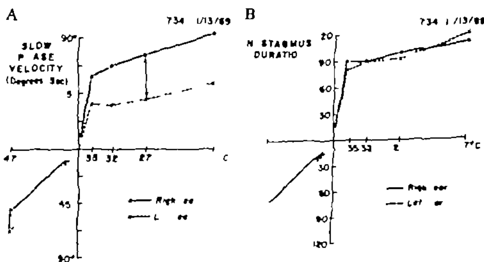


Fig 56 Graphs of slow phase velocity (A) and duration (B) of caloric nystagmus shown in Figure 55 This monkey (734) had strong directional preponderance of nystagmus to the left which was manifest in slow phase velocity (A) but was not expressed in nystagmus duration (B)

present after lesions of the dorsal medullary reticular formation

There is no clear explanation for the long-lasting positional nystagmus in 586 734 with a larger lesion in the same area did not have positional nystagmus Despite the close proximity of MVN and the dorsal medullary reticular formation the differences in oculomotor and postural changes after lesions show that these regions must function quite separately

CALORIC STIMULATION 734 (11/13/69)

RIGHT EAR LEFT EAR

17 C

27° C

32 C

35 C

47 C

10 sec

Fig 55 Nystagmus induced by stimulation of the right and left ears with different water temperatures in 734 The top trace is the horizontal EOG the second trace is slow phase velocity and the bar under the slow phase velocity trace shows the duration of stimulation. The vertical bars are 22° for the horizontal EOG and 45°/sec for the slow phase velocity

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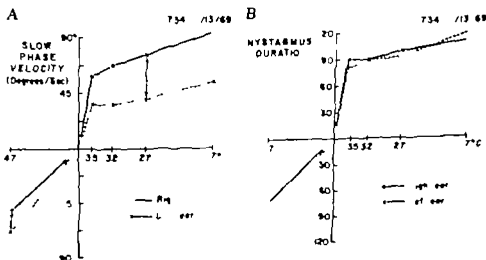


Fig 56 Graphs of slow phase velocity (A) and duration (B) of caloric nystagmus shown in Figure 55 The monkey (734) had strong directional preponderance of nystagmus to the left which was manifest in slow phase velocity (A) but was not expressed in nystagmus duration (B).

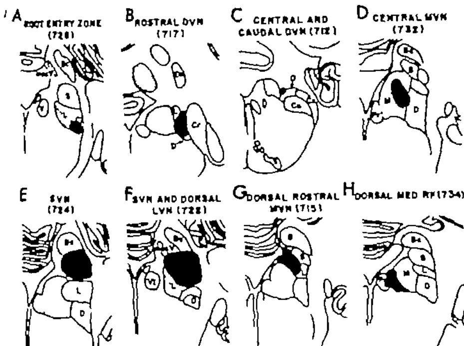


Fig 57 Diagrams of lesions in 728 (A), 717 (B), 712 (C), 732 (D), 734 (E), 722 (F), 715 (G), and 734 (H)

of afferent pathways from the cerebellum to SVN and possibly to the reticular formation It seems unlikely that dorsal LVN plays a significant role in mediating vestibulo-ocular reflexes

Horizontal caloric nystagmus was strongly affected by the nerve root lesion in 728 and the nerve root-rostral DVN lesion in 717 In both animals the lesions caused heavy degeneration of fibers in ventral LVN Rostral DVN was unaffected in 728 Since the defect in caloric nystagmus was not worse after the addition of the rostral DVN lesion in 717 we would infer that changes in caloric nystagmus in this animals were not related to the destruction of this nucleus but were due to the loss of vestibular nerve fibers which project to ventral LVN A similar loss of horizontal caloric nystagmus did not occur after lesions of other parts of the vestibular complex. This suggests that ventral LVN is an important primary projection area for afferent information from the lateral semicircular canals which induces horizontal caloric nystagmus

There has been little information to date about what role if any ventral LVN might play in mediating ocular reflexes from the semicircular canals or otolith organs Peterson (1970) found units in ventral LVN which were related to head tilt indicating some relation of ventral LVN to the otolith organs On the other hand Sans et al (197?) found that most units in ventral LVN *which* were monosynaptically linked to the vestibular apparatus were excited by semicircular canal nerve stimulation Desole & Pallestrini (1969) suggested that neurons in this area were *only* nonspecifically activated by the semicircular canals One possible *source of* confusion in interpreting *the results in* various unit studies is that the extent of ventral LVN is usually not *indicated in* any detail and differences in *defining the limits* of this nucleus could cause considerable apparent variation in results.

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10 General Discussion

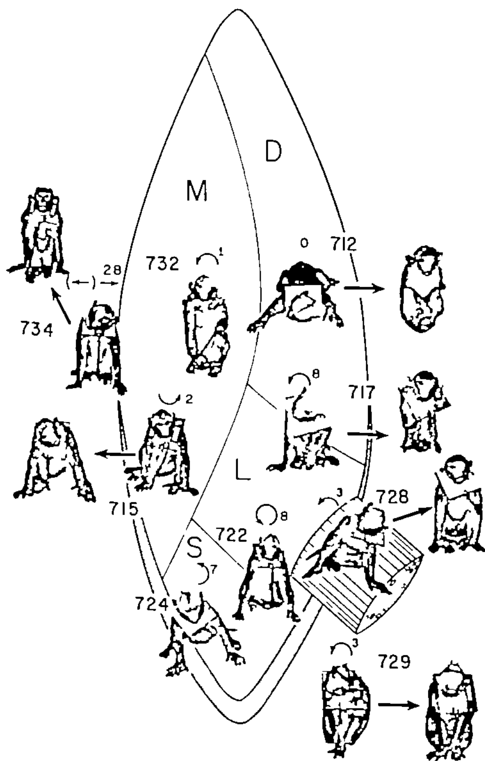
A PHYSIOLOGICAL IMPLICATIONS

Analysis of a complex sensory motor control system cannot be accomplished by anatomic or electrophysiological techniques alone The system must also be viewed from the stand point of performance or of changes in per formance after lesions of its component parts In previous studies of changes in vestibulo-ocular reflexes after vestibular nuclei lesions there was inadequate localization of lesions or inadequate description of the results of testing In this report we have attempted to show the extent of the lesions in several planes and to present objective evidence wherever possible to demonstrate the changes in eye movements In relation to the complexity of the vestibular nuclei and of vestibulo-ocular reflexes the number of animals with lesions was small and the testing techniques were relatively limited in scope For example the posterior semicircular canals were probably not tested (Fig 3 Chapter 2) Neither angular nor linear movement was used nor was counter rolling elicited Therefore this must be considered in the nature of a pilot study However a number of tentative conclusions and speculations can be made about oculomotor and postural function of the vestibular nuclei from the data

According to the different effects of lesions on eye movements and posture the vestibular nuclei can be subdivided into a number of regions These include (1) root entry zone and ventral LVN (2) dorsal LVN (3) rostral DVN (4) caudal DVN (5) SVN (6) rostral MVN (7) central or caudal MVN Differences in test findings have also been noted after lesions of the dorsal medullary tegmentum near the prepositus hypoglossi The effects of lesions in several of these regions will be discussed separately To aid in this discussion lesions in some of the most important animals are summarized in Fig 57 Postural changes and spontaneous nystagmus after lesion and after contralateral labyrinthectomy in these animals are shown in Fig 58 The monkeys are placed on a diagram of the vestibular nuclei over the approximate location of their lesions Photographs of 717 which had a right sided lesion were reversed to be consistent with the other animals The thin arrows and numbers over each monkey s head show the direction and duration of the spontaneous nystagmus The heavy arrows point to the posture after contralateral labyrinthectomy

The lateral vestibular nucleus None of the animals had isolated destruction of LVN but some deductions can be made about the function of this nucleus The afferent input and vestibulo-spinal projections of dorsal and ventral portions of LVN are different (Pompeiano & Brodal 1957 a Walberg et al 1958 Pompeiano 1960 Ito et al 1964 1969 Nyberg Hansen & Mascitti 1964 Wilson et al 1966 1967 *a*) Findings in 727 and 728 support this subdivision

In 728 the gliosis and fiber loss in LVN after destruction of the vestibular nerve trunk at the root entry zone was limited to the ventral part (728 Fig 57 A) This is in agreement with Walberg et al s (1958) conclusions that primary vestibular afferents enter ventral not dorsal LVN After a lesion of the restiform body in 727 gliosis and demyelination due to interruption of cerebello-vestibular pathways was prominent in the dorsal part of LVN and in SVN Ventral LVN was unaffected Changes in oculomotor function in 727 could be attributed to interruption



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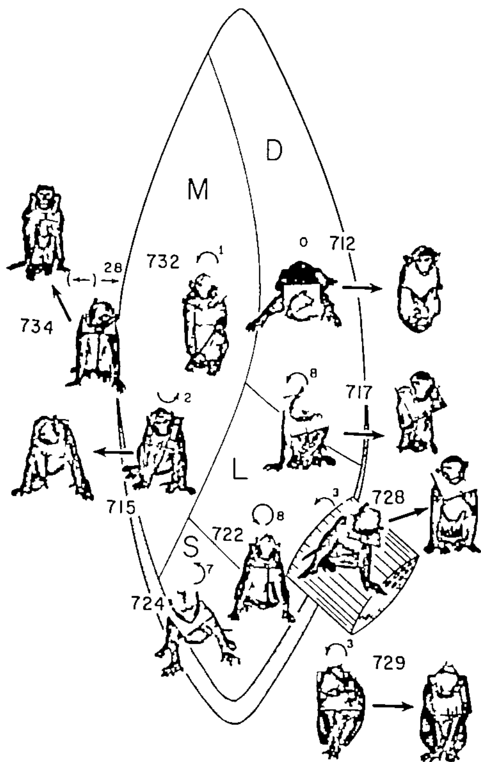
Similarly although projections from ventral LVN to the spinal cord are well known there is some controversy as to whether or not LVN projects to eye muscle motor nuclei Electric stimulation in the region of ventral LVN caused horizontal nystagmus in the cat (Yules & Gault 1966) McMasters et al (1966) demonstrated projections from ventral LVN to the motor nucleus of the ipsilateral medial rectus and contralateral lateral rectus muscles in the monkey These muscles would cause the eyes to move in the horizontal plane Tarlov (1970) denied the presence of projections from LVN to eye muscle motor nuclei in the cat However Gacek (1971) found projections from ventral LVN to both the abducens nucleus and the dorso-lateral cell group of the ipsilateral oculomotor nucleus in the cat The dorso-lateral cell group innervates the medial rectus muscle in this animal (Tarlov & Tarlov 1971)

PAN was preserved after contralateral labyrinthectomy in 728 It seems likely that ventral LVN is not a major receiving area for primary afferents from the otolith organs responsible for PAN Presumably the majority of these fibers enter rostral DVN The separation of lesions which affect horizontal caloric nystagmus and PAN is somewhat against the conclusion of Money et al (1965) and Nito et al (1964 1968) that PAN originates in the lateral semicircular canals

The descending vestibular nucleus On the basis of oculomotor and postural effects of lesions DVN appears to be subdivided into a rostral and caudal part A lesion of rostral DVN (717 Fig 57 B) caused a marked head tilt to the ipsilateral side (Fig 58 717) contralateral horizontal rotatory spontaneous nystagmus and a loss of positional effects on spontaneous nystagmus and PAN following contralateral labyrinthectomy The loss of positional effects on spontaneous nystagmus and on PAN suggests that rostral DVN is directly concerned with processing information from the otolith organs for vestibulo-ocular reflexes This agrees with the anatomical findings that rostral DVN receives primary vestibular afferents from the utricle (Stein & Carpenter 1967) It is also consistent with data of Peterson (1970) that units in rostral DVN had the greatest sensitivity to lateral head tilt There was relatively little influence of the caudal DVN lesion (Fig 57 C) on spontaneous nystagmus and caloric responses and PAN was preserved after contralateral labyrinthectomy We would infer that caudal DVN is not a primary sensory receiving area for vestibulo-ocular information arising either in the semicircular canals or in the otolith organs

The route by which activity from rostral DVN reaches the oculomotor nuclei is unclear Pompeiano & Walberg (1957) showed that there were retrograde cell changes in rostral DVN after MLF lesions On the other hand little or no degeneration has been found in the ascending MLF or oculomotor nuclei after rostral DVN lesions in a number of studies (McMasters et al 1966 Tarlov 1970 Gacek 1971) Another possible route for activity from rostral DVN to the eye muscle motor nuclei is through the cerebellum Brodal & Torvik (1957) have shown that caudal DVN projects to the vestibulo-cerebellum and Angaut & Brodal (1967) that caudal DVN receives afferent projections from the nodulus and uvula They suggest the existence of a loop between the nodulus and uvula and cau

Fig 58 Pictures of head position and body posture after lesion and in some monkeys after contralateral labyrinthectomy The lesions are all shown on the left side The monkeys are identified by numbers and are positioned over the left vestibular nuclear complex in the appropriate area of the destruction The small arrows indicate the direction of the spontaneous nystagmus and the small numbers the number of days the nystagmus was present in light The heavy arrows point to the head position and body posture after contralateral (right) labyrinthectomy 734 had gaze nystagmus to the left for 28 days and temporary spontaneous nystagmus to the right (shown by the arrow in parentheses) 739 first had a left labyrinthectomy and then the right labyrinth was destroyed



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dal DVN The cerebellum in turn has direct pathways to vertical and vertical rotatory eye movers (Carpenter & Strominger 1964 Highstein 1971 1973 a Highstein et al., 1971)

Apogeotropic direction-changing positional nystagmus was striking after caudal DVN destruction in 712. However it was still possible to produce nystagmus to either side during PAN I after the contralateral labyrinth had been destroyed Thus caudal DVN could not be essential for preservation of PAN It is possible that caudal DVN plays a role in modulating or inhibiting otolith-ocular reflexes

There was also evidence for a functional separation of rostral and caudal DVN from their different effects on posture The monkey with a rostral DVN lesion had an ipsilateral falling tendency and head tilt (Fig 58 717) Its neck muscles appeared to be strongly affected After a caudal DVN lesion there was severe dysequilibrium which appeared to be more closely related to changes in lumbar and hindlimb musculature (Fig. 58 712) Similar postural changes were described by Carpenter et al (1960) in the cat after DVN destruction

Present knowledge is insufficient to explain the different postural effects of rostral and caudal DVN lesions or of any DVN lesions for that matter According to anatomical studies DVN does not project directly to the spinal cord (Carpenter 1960 Carpenter et al 1960 Nyberg-Hansen & Mascitti 1964 Nyberg Hansen 1964) However Wilson et al (1967b) and Kawai et al. (1969) found cells in medial DVN with axons which descended to the spinal cord so that presumably such connections exist Other possibilities are that the postural changes were mediated over multi-synaptic pathways or through the cerebellum. Spino-vestibular projections to DVN only reach the most caudal portions (Pompeiano & Brodal 1957 b Brodal & Angaut, 1967) This may mean that the same type of organization is present in DVN as in LVN (Brodal et al 1962) That is parts of LVN which receive primary vestibular afferents (ventral LVN) project more heavily to the cervical spinal cord while portions which receive spinal afferents (dorsal LVN) project more heavily to the lumbo-sacral cord

The superior vestibular nucleus It is generally assumed that oculomotor function is predominantly represented in SVN The striking postural changes in 724 (Fig 58) indicate that this nucleus may also exert some control over body posture The pathways over which this control might be mediated are unknown

The horizontal component of induced caloric nystagmus was preserved after total SVN destruction Therefore SVN could not be essential for production of horizontal caloric nystagmus On the other hand eye movements induced by SVN stimulation (Tokumasu et al 1969) and spontaneous nystagmus following SVN destruction were in planes parallel to the plane of the ipsilateral anterior semicircular canal or the contralateral posterior canal This suggests that SVN plays a role in mediating activity between the anterior canals and the eye muscle motor nuclei. Downward eye movements were never induced by SVN stimulation (Tokumasu et al 1969).

The oculomotor projections of SVN are in accord with this hypothesis. In the monkey the projection of SVN is ipsilateral (McMasters et al. 1966) and is heaviest to motoneurons innervating the contralateral *superior oblique* and the ipsilateral inferior rectus muscles. Projections from SVN only carry inhibition (Highstein & Ito 1971 Highstein et al 1971 Precht & Baker 1972) If the ipsilateral inferior rectus and contralateral superior oblique muscles are inhibited the ipsilateral eye moves up and the contralateral eye moves up and extorts. These are exactly the eye movements induced by stimulation of the ipsilateral anterior canal nerve (Cohen et al 1964 Suzuki et al. 1964 Suzuki & Cohen 1964) or of SVN (Tokumasu et al 1969) and are just the reverse of the slow phases

to the cervical spinal cord (Wilson et al. 1968 *a*) in the medial vestibulo-spinal tract (Nyberg-Hansen, 1964 1966) These afferents mainly mediate inhibition onto cervical motoneurons (Wilson & Yoshida 1969 *a*) Excitatory inputs on the same motoneurons come from LVN via the lateral vestibulo-spinal tract (Wilson & Yoshida, 1969 *b*) Head tilt was stronger after nerve root destruction in 728 which caused degeneration in parts of LVN which project to the cervical spinal cord (Pompeiano & Brodal 1957 *a*) This may indicate that a loss of excitation causes more manifest postural changes than a loss of inhibition.

With one exception none of the monkeys had positional nystagmus after MVN lesions and PAN was preserved after contralateral labyrinthectomy It does not appear that MVN is of primary importance in processing information in otolith-ocular reflex arcs

Anatomical findings suggest that there is a functional separation between rostral and central MVN Rostral MVN together with SVN is a major terminus of afferent fibers from the semicircular canals (Stein & Carpenter 1967 Gacek, 1969) This region sends axons to eye muscle motor nuclei through the MLF and commissural fibers (McMasters et al 1966 Tarlov 1970 Gacek 1971). Central and caudal MVN does not receive primary afferent vestiblar fibers nor does it project to the oculomotor system Angaut & Brodal (1967) have also separated rostral and caudal MVN based on the distribution of fibers from the flocculus and nodulus The separation of rostral and central MVN is in accord with results of caloric testing Monkeys with lesions of rostral MVN exhibited perverted caloric nystagmus This did not occur after central MVN destruction

There are both excitatory and inhibitory projections from rostral MVN to eye muscle motor nuclei (Baker et al 1969 Highstein et al Highstein 1971 1973 *a* 1973 *b* Precht & Baker 197? Richter & Prect 1968) MVN also sends axons to the contralateral vestibular nuclei in the commissural system which are primarily inhibitory (Ladpli & Brodal 1968 Shimazu & Precht 1966) The pattern of vestibulo-oculomotor projections from MVN is complex and is not related solely or predominantly to eye movements in any single plane (McMasters et al. 1966 Tarlov 1970 Gacek, 1971)

In view of the heavy input from the semicircular canals it is surprising that the spontaneous nystagmus was not stronger and that the changes in caloric nystagmus were not more protean after the rostral MVN lesions The main changes in nystagmus were an enhancement of vertical components (perverted nystagmus) and loss of the horizontal component of nystagmus induced by hot caloric stimulation i.e by an increase of activity in the lateral canal nerve It is possible that the MVN lesions were too small to cause greater effects. On the other hand portions of the nuclei which were destroyed in 4 animals (Fig 43 Fig 44) are just those parts of MVN which receive primary afferents from the semicircular canals (Stein & Carpenter 1967 Gacek, 1969) and a stronger effect on caloric nystagmus induced by cold stimulation would have been expected

The horizontal components of nystagmus induced by ipsilateral hot stimulation were lost for more than 3 *months* in 588 Despite this the horizontal components induced by cold caloric stimulation were unaffected. This suggests that rostral MVN may be important in generating or controlling horizontal slow phases induced by increasing activity in the ampullary nerve from the lateral canal, although the nature of this control is still unclear

Perverted caloric nystagmus in 700 701 and 715 after dorso-rostral MVN lesions was similar to that found in 724 after SVN destruction (Fig. 47) In 588 after more extensive rostral MVN damage the perversion was more severe and was induced by ipsilateral hot as well as by contralateral hot and cold stimulation. This suggests that the enhanced vertical caloric

of spontaneous nystagmus after SVN destruction Gacek (1971) also found an entirely ipsilateral projection from SVN in the cat If sites of termination in the oculomotor nucleus are interpreted according to findings of Tarlov & Tarlov (1971) then mainly the *contralateral superior oblique* and the ipsilateral inferior rectus and inferior oblique receive projections from SVN in this animal as well

SVN cannot be the only part of the vestibular nuclei responsible for eye movements in anterior canal planes since it was still possible to evoke vertical caloric nystagmus by bilateral simultaneous stimulation after total SVN destruction Moreover Tokumasu & Goto (unpub results) destroyed SVN in the cat and were still able to induce upward rotatory eye movements from stimulation of the ipsilateral anterior canal nerve Presumably the pathway carrying excitatory activity from the anterior canals goes through other parts of the vestibular nuclei

Enhancement of vertical rotatory components of caloric nystagmus induced by stimulation of the contralateral ear was striking after SVN and MVN lesions As noted in the Section on Interpretation of Vertical Caloric Responses the horizontal component of caloric nystagmus predominates in normal animals even though the anterior canal is concommitantly stimulated The plane of the perverted nystagmus was parallel to the plane of the anterior canal on the side which was calorically stimulated The most likely explanation for the perverted nystagmus is that there was a loss of suppression of anterior canal responses From the lesion data it seems likely that this suppression originated in SVN and MVN and projected to the vestibular nuclei on the contralateral side After SVN and MVN lesions this suppression was lost and the dysinhibited response of the anterior canals appeared

As noted in the Introduction Ladpli & Brodal (1968) have shown that vestibular commissural fibers originate in SVN and MVN and cross the brain stem to distribute to the four vestibular nuclei on the opposite side The vestibular commissural system mediates inhibition in most of its projections (Shimazu & Precht 1966 Wilson et al 1968 *b* Kasahara et al 1968 Mano et al 1968) Therefore the physiological and anatomical substrate for crossed inhibition exists although it has not been tied to suppression of anterior canal activity Perverted caloric responses due to anterior canal excitation after SVN lesions would be another line of evidence which suggests that SVN is closely related to anterior canal function or to representation of eye movements in planes of space parallel to the anterior canal

Although SVN receives primary vestibular afferents mainly from the semicircular canals, positional nystagmus was present after SVN lesions This shows that SVN must also play a role in mediating or modulating otolith-ocular reflexes Positional nystagmus after SVN lesions could not have come from interruption of primary afferents from the utricle and saccule since there are few (Stein & Carpenter 1967) or none of these axons which terminate in SVN (Gacek 1969) On the other hand SVN receives axons from the flocculus the nodulus and the uvula (Angaut & Brodal 1967 Voogd 1964) as well as from the fastigial nucleus (Walberg et al 1962) It seems likely that the interruption of afferent cerebello-vestibular fibers in addition to destruction of SVN itself was important in causing the positional nystagmus found in monkeys with SVN lesions As noted there is also a close relationship between caudal DVN and the nodulus and uvula and positional nystagmus was also present after lesions of these structures

The medial vestibular nucleus The role of MVN in maintenance of posture or production of eye movements is not elucidated by our findings Postural abnormalities were minimal after lesions of either rostral or central MVN (Fig 57 D G Fig 58 715 732) These portions of MVN send afferents

to the cervical spinal cord (Wilson et al 1968 *a*) in the medial vestibulo-spinal tract (Nyberg-Hansen 1964 1966). These afferents mainly mediate inhibition onto cervical motoneurons (Wilson & Yoshida 1969 *a*) Excitatory inputs on the same motoneurons come from LVN via the lateral vestibulo-spinal tract (Wilson & Yoshida 1969 *b*) Head tilt was stronger after nerve root destruction in 728 which caused degeneration in parts of LVN which project to the cervical spinal cord (Pompeiano & Brodal, 1957 *a*) This may indicate that a loss of excitation causes more manifest postural changes than a loss of inhibition

With one exception none of the monkeys had positional nystagmus after MVN lesions and PAN was preserved after contralateral labyrinthectomy It does not appear that MVN is of primary importance in processing information in otolith-ocular reflex arcs

Anatomical findings suggest that there is a functional separation between rostral and central MVN Rostral MVN together with SVN is a major terminus of afferent fibers from the semicircular canals (Stein & Carpenter 1967 Gacek 1969) This region sends axons to eye muscle motor nuclei through the MLF and commissural fibers (McMasters et al 1966 Tarlov 1970 Gacek, 1971). Central and caudal MVN does not receive primary afferent vestiblar fibers nor does it project to the oculomotor system. Angaut & Brodal (1967) have also separated rostral and caudal MVN based on the distribution of fibers from the flocculus and nodulus The separation of rostral and central MVN is in accord with results of caloric testing. Monkeys with lesions of rostral MVN exhibited perverted caloric nystagmus. This did not occur after central MVN destruction

There are both excitatory and inhibitory projections from rostral MVN to eye muscle motor nuclei (Baker et al 1969 Highstein et al. Highstein 1971 1973 *a* 1973 *b* Precht & Baker 1972 Richter & Precht 1968) MVN also sends axons to the contralateral vestibular nuclei in the commissural system which are primarily inhibitory (Ladpli & Brodal 1968 Shimazu & Precht, 1966) The pattern of vestibulo-oculomotor projections from MVN is complex and is not related solely or predominantly to eye movements in any single plane (McMasters et al 1966 Tarlov 1970 Gacek, 1971)

In view of the heavy input from the semicircular canals it is surprising that the spontaneous nystagmus was not stronger and that the changes in caloric nystagmus were not more protean after the rostral MVN lesions The main changes in nystagmus were an enhancement of vertical components (perverted nystagmus) and loss of the horizontal component of nystagmus induced by hot caloric stimulation i e by an increase of activity in the lateral canal nerve It is possible that the MVN lesions were too small to cause greater effects On the other hand portions of the nuclei which were destroyed in 4 animals (Fig. 43 Fig. 44) are just those parts of MVN which receive primary afferents from the semicircular canals (Stein & Carpenter 1967 Gacek, 1969) and a stronger effect on caloric nystagmus induced by cold stimulation would have been expected.

The horizontal components of nystagmus induced by ipsilateral hot stimulation were lost for more than 3 months in 588 Despite this the horizontal components induced by cold caloric stimulation were unaffected. This suggests that rostral MVN may be important in generating or controlling horizontal slow phases induced by increasing activity in the ampullary nerve from the lateral canal although the nature of this control is still unclear

Perverted caloric nystagmus in 700 701 and 715 after dorso-rostral MVN lesions was similar to that found in 724 after SVN destruction (Fig. 47) In 588 after more extensive rostral MVN damage the perversion was more severe and was induced by ipsilateral hot as well as by contralateral hot and cold stimulation. This suggests that the enhanced vertical caloric

of spontaneous nystagmus after SVN destruc tion Gacek (1971) also found an entirely ipsilateral projection from SVN in the cat If sites of termination in the oculomotor nucleus are interpreted according to findings of Tarlov & Tarlov (1971) then mainly the contralateral superior oblique and the ipsi lateral inferior rectus and inferior oblique receive projections from SVN in this animal as well

SVN cannot be the only part of the vestibular nuclei responsible for eye movements in anterior canal planes since it was still possible to evoke vertical caloric nystagmus by bilateral simultaneous stimulation after total SVN destruction Moreover Tokumasu & Goto (unpub results) destroyed SVN in the cat and were still able to induce upward rota tory eye movements from stimulation of the ipsilateral anterior canal nerve Presumably the pathway carrying excitatory activity from the anterior canals goes through other parts of the vestibular nuclei

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Spontaneous nystagmus

Disconjugate defects such as are found after MLF lesions (Bender & Weinstein, 1944 Carpenter & McMasters 1963 Cohen, 1971) were not present in any of the animals of this series. Therefore disconjugate defects if present, are a sign of lesions outside the vestibular nuclei. Similarly gaze nystagmus was not prominent after lesions of the vestibular complex

Spontaneous nystagmus which followed left vestibular nuclei lesions was horizontal rotatory upward rotatory and pure rotatory in character Nystagmus with a downward component was not initially observed in any of the animals with vestibular nuclei lesions although in several animals the positional nystagmus was downward during the recovery course. The reason for the absence of downward spontaneous nystagmus is not known. In animals with left-sided lesions rotatory components were counterclockwise (Fig. 58) This is just opposite to the rotatory components of nystagmus induced by stimulation of the vestibular nuclei on the left side (Tokumasu et al 1969)

The horizontal component of the spontaneous nystagmus was contralateral after lesions of the nerve root and of caudal lateral parts of the vestibular nuclei After SVN and rostral MVN lesions on the other hand the horizontal component of the spontaneous nystagmus was ipsilateral. Thus is just the reverse of nystagmus induced by electrical stimulation of these parts of the vestibular nuclei i.e to the ipsilateral side with lateral stimulation and to the contralateral side with medial stimulation (see Figure 6 A of Tokumasu et al., 1969) Pure horizontal or vertical nystagmus was not present in any of the animals with vestibular nuclei lesions Bender (1960) has noted that vertical nystagmus in the mid-sagittal plane is most commonly associated with midline or bilateral brainstem lesions

The reversal in direction of spontaneous nystagmus from contralateral to ipsilateral side was noted in the EOG during the recovery course in monkeys with lesions of the root entry zone and rostral DVN as well as after unilateral labyrinthectomy Igarashi et al (1970) also found a change in the direction of falling on a rail test in squirrel monkeys after unilateral labyrinthectomy

Positional nystagmus

Positional nystagmus is associated with cerebellar lesions (Nylén 1931 1950 Spiegel & Scala, 1942 Fernández, 1960 Fernández & Fredrickson 1964 Cohen et al 1969 Cohen & Highstein 1972) vestibular nuclei lesions and lesions of cerebello-vestibular connections (727) Animals with lesions in two parts of the vestibular nuclei had direction-changing positional nystagmus After caudal DVN destruction there was apogeotropic direction-changing positional nystagmus which was mainly horizontal It was to the left with the right side down and to the right with the left side down. We have not observed apogeotropic or antigravity positional nystagmus after labyrinthectomy or after other vestibular nuclei lesions but it has been produced by lesions of the cerebellar nuclei (Cohen et al. 1969 Cohen & Highstein, 1972)

In contrast positional nystagmus associated with lesions of SVN had strong rotatory components, and the direction of rotation reversed in 722 and 724 when the head was put into different positions After flocculus lesions there is rotatory positional nystagmus in the coronal plane for about 1 week (Cohen & Takemori, 1973) This is of interest in view of the heavy projections from the flocculus to SVN Rotatory positional nystagmus is found in patients with benign paroxysmal vertigo However this nystagmus reverses when the patient is brought from the supine to the upright position, not when the head is to the left or right as in 724 or 722.

Direction-fixed positional nystagmus was also commonly induced in animals with vestibular nuclei lesions. It usually occurred in conjunction with the spontaneous nystag-

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The medullary reticular formation Evidence which suggests that the dorsal medullary reticular formation may play a role in ocular function is limited However Hyde & Eliasson (1957) found two areas in the brain stem of the cat from which horizontal eye movements could be induced by electrical stimulation One was *the tegmentum of the* pons which is known to be important for production of horizontal gaze (Bender & Shanzer 1964 Cohen 1971) The other was more caudal in the medulla When this area was destroyed strong directional preponderance of OKN and loss of OKAN was produced Further studies are needed to elucidate the extent of this region and its role in producing eye movements

B CLINICAL IMPLICATIONS

Changes in Posture

Only simple postural testing was done after *vestibular* nuclei *lesions* and disturbances in posture were probably underestimated The relative intensity of postural imbalance and of spontaneous nystagmus varied according to the parts of the vestibular nuclei which were damaged Nevertheless *the direction of the* falling tendency and head tilt following unilateral vestibular nuclei lesions was in accordance with the direction of the slow phases of spontaneous nystagmus This is shown in Figs 57 & 58 Monkeys with *lesions of lateral or* caudal parts of the vestibular nuclei (728 717 *712) or of the peripheral* apparatus (729 707) had head tilts to the ipsilateral side and spon*taneous nystagmus to the* contralateral side (ipsilateral slow phases) 724 and 715 with lesions of SVN and rostral MVN had some contralateral head tilt and an ipsilateral component to their spontaneous nystagmus 722 *with an intermediate lesion* had no head tilt

The coincidence of the direction of head tilt and falling tendency with the direction of the slow phases of spontaneous nystagmus after *vestibular nuclei lesions can be contrasted* to that observed after lesions outside the vestibular nuclei *Both the head tilt and* quick phases of nystagmus were directed to the ipsilateral side after dorsal *medullary* reticular formation lesions (734) and to the contralateral side after pontine reticular formation lesions (Cohen *et al* 1968) These differences in direction of postural deviation and spontaneous nystagmus may be of use in separating lesions in and around the vestibular nuclei Although coincidence of the direction of slow phases and falling tendency cannot be used to separate central from peripheral *vestibular lesions a falling tendency* in the same direction as the quick phases of nystagmus would appear to point to a lesion involving parts of the central nervous system outside the vestibular nuclei

The *most severe disturbances of posture* were noted after DVN lesions although dysequilibrium after *SVN destruction was also* strong Disturbances of equilibrium following lesions of the root entry zone were somewhat weaker *Despite the intimate relation*ship between MVN and the cervical spinal cord little change in posture was manifest after either rostral or central MVN destruction

Postural deficits due to unilateral vestibular lesions showed rapid attenuation within one month in all animals and in most monkeys there was only a minimal effect of subsequent destruction of the contralateral labyrinth *The contralateral labyrinthectomy also* had a smaller effect on posture than the initial labyrinthectomy in 707 and 729 Only in 715 was there a strong head tilt after contralateral labyrinthectomy (Fig 58) and it persisted unchanged until sacrifice 40 days later *Mechanisms to compensate for the head* tilt after contralateral labyrinthectomy ap*peared to be disturbed in this animal*

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This emphasizes the clinical importance of both hot and cold caloric stimulation when investigating patients with suspected vestibular nuclei lesions.

Optokinetic nystagmus

The loss of OKAN and changes in OKN after destruction of the vestibular apparatus (Cohen et al 1973) are of interest because they demonstrate the close relationship between the vestibular and visual systems in producing eye movements. In agreement with this, there was directional preponderance of OKN after unilateral vestibular nuclei lesions. This was always associated with spontaneous nystagmus and with directional preponderance of caloric nystagmus with positional nystagmus or with changes in PAN. OKN was less strongly affected than caloric nystagmus when lesions were inside the vestibular nuclei.

In contrast, lesions of the dorsal medullary reticular formation (586 734) and mesencephalic reticular formation (MRF) (Komatsuzaki et al. 197?) cause stronger changes in OKN than in caloric nystagmus. After MRF lesions there is frequently ipsilateral gaze preference and spontaneous nystagmus and an inability to generate contralateral OKN. Caloric nystagmus is relatively normal in these animals. Lesions of the paramedian zone of the pontine reticular formation (PPRF) are associated with an inability to produce quick phases of high velocity to the ipsilateral side (Cohen et al. 1968 Cohen & Henn 1972). PPRF lesions produce conjugate gaze paralysis which affects all types of nystagmus similarly regardless of how they were induced. Lesions in more distal parts of oculomotor pathways such as MLF lesions which produce paralysis of adduction (Bender & Shanzer 1964) or motor nuclei or nerve lesions also affect all types of nystagmus similarly

mus but at later stages in the recovery course could occur alone The observed nystagmus was similar in animals with labyrinthectomy or with lesions of the root entry zone In these monkeys (707 729 728) it was predominantly contralateral horizontal with the ipsilateral side down and rotatory with the contralateral side down The upside down position was most sensitive for eliciting positional nystagmus during recovery This is analogous to the head-hanging positions used in testing humans

Caloric nystagmus

Canal paresis was not found after SVN central and caudal DVN or rostral and central MVN lesions but was present after damage of the vestibular nerve at the root entry zone It was characterized by a decrease in the velocity of slow phases of nystagmus induced by cold and hot stimulation of the ipsilateral ear Duration of nystagmus was much less affected in animals which had canal paresis It has been suggested that the way in which duration and maximum slow phase velocity of caloric nystagmus are affected by vestibular lesions may give some idea as to the site of damage (Stahle 1956 Aschan & Stahle 1956) After vestibular neuronitis changes are mainly in parameters related to slow phase velocity and duration of nystagmus is affected only to a lesser extent In contrast disease of the peripheral labyrinth such as Menière s disease appears to affect all parameters of nystagmus similarly (Aschan & Stahle 1956)

It has been assumed that vestibular neuronitis is due to vestibular nerve damage but there has been no anatomical verification of this to our knowledge The findings in 728 show that lesions which partially destroy the nerve or nerve roots reproduce this constellation of signs This seems reasonable since duration of nystagmus is related to the time course of cupula deflection which in turn is dependent on the elasticity of the cupula. This would not be affected by nerve lesions On the other hand peripheral lesions which affect the cupula or hair cells would be expected to reduce all aspects of the response of the peripheral end organ

In animals with nerve root lesions stronger caloric stimuli i e those further away from body temperature did not recruit stronger caloric nystagmus If weaker stimuli were used the caloric nystagmus had nearly the same intensity from the intact as from the lesion side and differences in intensity of the induced response could be easily overlooked This is just the reverse of the response to weak and strong caloric stimulation after lesions of the labyrinth itself (Litton & McCabe 1966 Steffen et al 1970 Torok 1970 Mendel 1971)

Every animal with spontaneous nystagmus had some indication of directional preponderance in the caloric test It was not of value in differentiating the side or locus of the lesion The strong directional preponderance in 734 suppressed caloric nystagmus in one direction and mimicked a loss of recruitment although there was no canal paresis in this animal In 728 and 727 however no recruitment was observed even after reversal of the spontaneous nystagmus by contralateral labyrinthectomy

Perverted caloric nystagmus i e nystagmus with enhanced vertical components was present after SVN lesions or after rostral MVN lesions Similar perversion has been found after brain stem lesions (Stroud et al 1971) after interruption of the vestibular commissural fibers by midline section (Cohen & de Jong unpublished data) or after cerebral hemidecortication (Pasik et al 1960) It was not found after flocculus lesions or lesions of the reticular formation of the pons (Cohen et al 1968) or mesencephalon (Komatsuzaki et al 1972) It is important to note that in some animals perverted caloric nystagmus was induced only by hot caloric stimulation on the side contralateral to the lesion If both hot and cold stimulation were not used in these monkeys the findings would have been missed

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11 Conclusions

(1) Changes in body posture and in vestibulo-ocular reflexes were studied in monkeys after lesions of the vestibular nuclei and the peripheral vestibular apparatus Based on oculomotor and postural changes after vestibular nuclei lesions the vestibular nuclei were subdivided into separate areas These included ventral LVN dorsal LVN rostral DVN caudal DVN SVN rostral MVN and central caudal MVN

(2) Head tilt and falling tendency were to the ipsilateral side after lesions of lateral or caudal parts of the vestibular nuclei or after lesions of the labyrinth They were to the contralateral side after SVN or rostral MVN lesions Postural changes after central MVN lesions were slight The strongest postural effects were produced by lesions of caudal DVN

(3) Quick phases of nystagmus were not primarily affected by vestibular nuclear lesions All changes in eye movements were conjugate and disconjugate defects similar to those observed after MLF lesions were not produced by unilateral vestibular nuclei destruction

(4) Spontaneous nystagmus was commonly found after vestibular nuclei lesions It was of short duration in light but could persist in darkness for much longer periods of time The direction of the slow phases of spontaneous nystagmus agreed with the direction of the postural change in each of the animals Reversal of spontaneous nystagmus during the recovery course was also noted

(5) Direction fixed positional nystagmus was produced by labyrinthectomy and by lesions of the root entry zone and rostral DVN Positional effects on spontaneous nystagmus were lost after rostral DVN lesion and contralateral labyrinthectomy This finding is in accord with anatomic studies which indicate that rostral DVN is a primary receiving area for activity arising in the otolith organs

(6) Horizontal geotropic direction-changing positional alcohol nystagmus (PAN) was induced to both sides after unilateral labyrinthectomy PAN was lost after bilateral labyrinthectomy or after destruction of rostral DVN and the contralateral labyrinth The rostral DVN lesion had the same effect on positional nystagmus as on PAN This suggests that activity responsible for PAN arises mainly in the otolith organs not in the lateral semicircular canals and is mediated through rostral DVN

(7) Apogeotropic direction-changing positional nystagmus of the type commonly associated with central vestibular lesions cerebellar lesions or the second phase of positional alcohol nystagmus (PAN II) was found after caudal DVN lesion Rotatory direction-changing positional nystagmus was produced by SVN lesions Both caudal DVN and SVN have prominent vestibulo-cerebellar or cerebello-vestibular projections and positional nystagmus is produced by lesions of portions of the cerebellum where these projections originate or end The data support the hypothesis that the cerebellum plays an important role in controlling or mediating utriculo-ocular or sacculo-ocular reflex arcs

(8) Canal paresis i e a reduction in the response of the ipsilateral ear to cold or hot caloric stimulation and a loss of recruitment was found when the root entry zone was damaged After root entry zone lesions there was little effect on the duration of induced nystagmus Lesions of other portions of the vestibular nuclei did not produce these find-

ings This is experimental verification that the clinical syndrome of vestibular neuronitis is reproduced by lesions which affect the vestibular nerve or nerve root. The data indicate the importance of slow phase velocity in diagnosis of lesions of the peripheral and central vestibular system. By comparing effects of lesions on duration and slow phase velocity of induced caloric nystagmus it may be possible to differentiate lesions affecting the vestibular nerve from those which affect the labyrinth

(9) Spontaneous nystagmus after SVN lesions lay in the plane of the ipsilateral anterior canal. The spontaneous nystagmus after SVN destruction was just opposite in direction to that induced by electrical stimulation of SVN before lesion. Considering that all known projections from SVN are inhibitory the directions of the induced eye movements and spontaneous nystagmus agree with the known anatomic connections from SVN to the eye muscle motor nuclei. It is concluded that eye movements in planes parallel to that of the ipsilateral anterior canal are represented in SVN

(10) After lesions of SVN and rostral MVN characteristic changes in caloric nystagmus were noted. These consisted of an enhancement of vertical components of nystagmus induced by stimulation of the contralateral ear with hot or cold water From the directions of the induced nystagmus it was inferred that the enhanced vertical components were due to anterior canal activation Perverted nystagmus after MVN lesions was similar to that after SVN lesions with the exception that perverted nystagmus was also induced by stimulation of the ipsilateral ear with hot water It is postulated that the SVN or MVN lesions caused perverted nystagmus by interrupting commissural pathways which inhibit activity arising in the anterior canals i.e. the lesions caused dysinhibition of anterior canal responses

(11) OKN was not strongly affected by vestibular nuclei lesions but high velocity slow phases of OKN were impaired by labyrinthectomy Directional preponderance of OKN was present after vestibular nuclei lesions It was an accompaniment of spontaneous nystagmus and was equal to or less severe than the directional preponderance of caloric nystagmus OKAN which is prominent in the monkey was reduced to both sides after unilateral labyrinthectomy ipsilateral more than contralateral OKAN was abolished by bilateral labyrinthectomy The vestibular apparatus appears to be an essential structure for maintenance of OKAN

(12) Lesions of the dorsal medullary reticular formation caused head tilt and spontaneous nystagmus in the same direction. In contrast after vestibular nuclei lesions the head tilt and quick phases of spontaneous nystagmus were oppositely directed. Strong directional preponderance of OKN was present in animals with lesions in the dorsal medullary reticular formation and OKAN was lost. Directional preponderance of caloric nystagmus was less strong than that of OKN It is inferred that this portion of the reticular formation has oculomotor as well as body postural functions

11 Conclusions

(1) Changes in body posture and in vestibulo ocular reflexes were studied in monkeys after lesions of the vestibular nuclei and the peripheral vestibular apparatus Based on oculomotor and postural changes after vestibular nuclei lesions the vestibular nuclei were subdivided into separate areas These included ventral LVN dorsal LVN rostral DVN caudal DVN SVN rostral MVN and central caudal MVN

(2) Head tilt and falling tendency were to the ipsilateral side after lesions of lateral or caudal parts of the vestibular nuclei or after lesions of the labyrinth They were to the contralateral side after SVN or rostral MVN lesions Postural changes after central MVN lesions were slight The strongest postural effects were produced by lesions of caudal DVN

(3) Quick phases of nystagmus were not primarily affected by vestibular nuclear lesions All changes in eye movements were conjugate and disconjugate defects similar to those observed after MLF lesions were not produced by unilateral vestibular nuclei destruction

(4) Spontaneous nystagmus was commonly found after vestibular nuclei lesions It was of short duration in light but could persist in darkness for much longer periods of time The direction of the slow phases of spontaneous nystagmus agreed with the direction of the postural change in each of the animals Reversal of spontaneous nystagmus during the recovery course was also noted

(5) Direction fixed positional nystagmus was produced by labyrinthectomy and by lesions of the root entry zone and rostral DVN Positional effects on spontaneous nystagmus were lost after rostral DVN lesion and contralateral labyrinthectomy This finding is in accord with anatomic studies which indicate that rostral DVN is a primary receiving area for activity arising in the otolith organs

(6) Horizontal geotropic direction-changing positional alcohol nystagmus (PAN) was induced to both sides after unilateral labyrinthectomy PAN was lost after bilateral labyrinthectomy or after destruction of rostral DVN and the contralateral labyrinth The rostral DVN lesion had the same effect on positional nystagmus as on PAN This suggests that activity responsible for PAN arises mainly in the otolith organs not in the lateral semicircular canals and is mediated through rostral DVN

(7) Apogeotropic direction-changing positional nystagmus of the type commonly associated with central vestibular lesions cerebellar lesions or the second phase of positional alcohol nystagmus (PAN II) was found after caudal DVN lesion Rotatory direction-changing positional nystagmus was produced by SVN lesions Both caudal DVN and SVN have prominent vestibulo-cerebellar or cerebello-vestibular projections and positional nystagmus is produced by lesions of portions of the cerebellum where these projections originate or end The data support the hypothesis that the cerebellum plays an important role in controlling or mediating utriculo-ocular or sacculo-ocular reflex arcs

(8) Canal paresis i e a reduction in the response of the ipsilateral ear to cold or hot caloric stimulation and a loss of recruitment was found when the root entry zone was damaged After root entry zone lesions there was little effect on the duration of induced nystagmus Lesions of other portions of the vestibular nuclei did not produce these find

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SUPPLEMENTUM 317

EPISTAXIS

A clinical study with special reference to fibrinolysis

By

BJÖRN PETRUSON

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From the Department f Otorhinolaryngology (Head Professor G Herberts, M.D.)
and the Coagulation Laboratory Department f Medicine II (Head Docent K. Korsan-Bengtsen, M.D.)
University f Göteborg, Sweden

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GÖTEBORG 1974

CONTENTS

INTRODUCTION

In the antique medicine as well as in most primitive cultures bleeding from the nose has been concepted with great curiosity. To-day we look upon epistaxis in a less mysterious way but still it is an uncomfortable experience upsetting and frightening the patient.

About 60 per cent of the subjects in a western population have suffered from nose bleedings at least once during life. Patients with bleeding from the nose are frequently observed in the daily work at the office as well as in the emergency clinic.

Significant for the symptom nose bleeding is great variation. A few drops of blood once in life might be described by one individual, repeated large spontaneous bleedings of long duration by another.

The cause and cource of epistaxis are probably multifactorial. Some etiological factors might explain the start of the nose bleeding, other factors the long duration and the recurrency of the bleeding. Still other factors might predispose to epistaxis. It must however be realized that a factor might predispose to epistaxis at the same time as it might explain a long duration and recurrency of bleeding.

The present investigation comprises a series of clinical and experimental studies centrated around the following questions:

Why does the nose bleeding start?
What are the predisposing factors?
What is the mechanism influencing the duration of the bleeding and why are some nose bleedings recurrent?

that 59 per cent of the out patients had had episodes of epistaxis for more than one year. In 22 per cent the actual bleeding was the first bleeding in life.

In hospitalized patients Derbeneva (1970) noted that 7 per cent of the patients suffered from recurrent epistaxis and that 31 per cent bled for the first time in life.

Seasonal variations. In most studies more patients with epistaxis were treated during winter than summer months (Hara 1962, Pierce and Chasin 1962, Serafini 1965, Popiel 1969).

B. Etiology of epistaxis

Upper respiratory infections. The frequency of upper respiratory infections before the epistaxis started has been investigated in several studies (table 1). The great variation of frequency in these studies – between one and a hundred per cent – depends most likely on the principle of selection of the patients and the use of different definitions of upper respiratory infection.

Acetylsalicylic acid. Tucker (1963) is the only author who has reported about the correlation between intake of acetylsalicylic acid and epistaxis. He noted that 4 per cent of the patients had taken acetylsalicylic acid before the bleeding started but regarded this to be coincidental.

In contrast to this, Parry and Wood (1967) discovered that 33 per cent of a control group (patients who visited a hospital due to other diseases than gastro-intestinal haemorrhage) had taken acetylsalicylic acid the week prior to the visit to the hospital.

Hypertension. The association between hypertension and epistaxis was investigated in different studies (Woodruff 1949, Hallberg 195 , Hara 196.., Pierce and Chasin 1962, Tucker 1963, Grabowski 1965, Serafin 1965, Phillip and von Harder 1966, Popiel 1969). It is difficult to draw conclusions from the result of these studies as neither control groups are studied nor definitions of hypertension are given.

I two studies (Mitchell 1959 and Shaheen 1970) the blood pressure in the patients with epistaxis was compared with the blood pressure of subjects in control groups. Mitchell found that the diastolic blood pressure was significantly higher in patients who had epistaxis (with no other nasal disease) than in the control group. The blood pressure was, however, not recorded in 75 per cent of the patients. In contrast to this Shaheen did not find any difference in blood pressure between his patients and a control group.

In the Health Examination Survey of adults 1960–62 (USA), the blood pressure was measured in 6 67 subjects. When the prevalence of different blood pressures was compared with the occurence of epistaxis no correlation was found between subjects with low and high blood pressure and histories of epistaxis (Weiss 197?).

Hematological diseases. In textbooks of hematology (for instance Videbaek 1965) it is said that diseases with defects in the hemostasis and malignant hematopoetic tumours often have epistaxis as a leading symptom.

When patients with epistaxis have been examined, malignant hematopoetic tumours have been reported in one to four per cent and defects in the hemostasis in one to a hundred per cent of the examined patients (table 3). In those studies where the patients were extensively examined with several tests (Laeber and Heinrich 1960, Maurer and Ruhl 1965) more defects in the hemostasis were found.

C. Localisation of the bleeding source

Although the age of the patient is of importance for the localisation of the bleeding source, many results are presented without regard to the age distribution of the patients.

In only one study on 136 hospitalized patients (Ogura and Senturia 1949) was the age distribution presented. All patients less than 15 years old had bleedings from the anterior part of the septum and 60 per cent of the patients more than 40 years of age had bleedings from posterior and lateral parts of the nasal cavity.

Hallberg (195) studied hospitalized patients with severe epistaxis. In 27 per cent of the patients the bleeding source was localized in the Kiesselbach area and in 17 per cent in other parts of the septum. The bleeding source was seen in other visible parts of the nasal cavity in 33 per cent and was invisible in 23 per cent of the patients.

In out patients examined by Tucker (1963) 74 per cent of the patients had bleedings from septum, 10 per cent bled from other visible parts of the nose and in 16 per cent of the patients the bleeding source was not visible.

CHAPTER I

REVIEW OF THE LITERATURE

Several studies have been published about etiological factors of epistaxis In the first part of this review the results of etiological analyses from some of the most important clinical studies are presented The results are chosen to serve as references to the present investigation

In the second part different treatments of epistaxis are analysed A third part contains a short review of the vascular anatomy of the nasal mucosa. Finally a short review of the physiology of hemostasis is presented

A Incidence of epistaxis

The incidence of epistaxis in a population sample (U S A) has been studied by Weiss (1972) who found that 7 to 14 per cent of the subject had had epistaxis at least once

A higher frequency of epistaxis in men than in women was noted by Hara (1962) and Tucker (1963) In contrast to this Grabowski (1965) and Popiel (1969) *found the same frequency in men as* in women

In out patients Tucker (1963) reported that 1? per cent of the patients were more than 60 years old and 43 per cent less than ?0 years old In hospitalized patients Hallberg (1952) Hara (196?) and Popiel (1969) noted that 40 respectively 35 and 26 per cent of the patients were more than 60 years old

It is difficult to draw any conclusions about the sex and age distribution of patients treated for epistaxis as the distribution in the population is unknown

Recurrent bleedings. Tucker (1963) reported

Table 1 The frequency of upper respiratory infections (URI) defects in the hemostasis (def hem) and malignant hematopoetic tumours (mal. hem) observed in some clinical studies of epistaxis. The studies were on out p tients (0) or on hospitalized patients (H)

Author		Number of patient			
		in the study	with URI (%)	with def hem (%)	with mal. hem (%)
Nevert et al 1948	O	104	1 (1%)	60 (59 %)	1 (1%)
Boeninghaus 1959	O	147		?	
Laeber and Heinrich 1960	O	40	?	30 (75 %)	
Tucker 1963	O	164	(21%)	0	0
Maurer and R hl 1965	O	31	31 (100 %)	31 (100 %)	
Phillip and von Harder 1966	O	336	77 (24 %)		
Timm 1966	O	284	(33%)	?	
Hallberg 1952	H	212	9 (4 %)	2 (10 %)	
Hara 1962	H	1 404	84 (6%)	118 (8%)	54 (4%)
Pierce and Chasin 196	H	13	?		5 (4%)
Grabowski 1965	H	102	2 (21 %)	1 (1%)	1 (1%)
Grunwald 1966	H	34	13 (26 %)	?	
Saraya and Kacker 1966	H	24		5 (21%)	4 (2%)
Popiel 1969	H	22	(25 %)		
Derbeneva 1969	H	640	10 (2%)		
Serafini 1965	?	606	87 (14 %)	10 (2 %)	

increase during influenz epidemic

that 59 per cent of the out patients had had episodes of epistaxis for more than one year. In 22 per cent the actual bleeding was the first bleeding in life.

In hospitalized patients Derbeneva (1970) noted that 7 per cent of the patients suffered from recurrent epistaxis and that 31 per cent bled for the first time in life.

Seasonal variations. In most studies more patients with epistaxis were treated during winter than summer months (Hara 1962, Pierce and Chasin 1962, Serafini 1965, Popel 1969).

B. Etiology of epistaxis

Upper respiratory infections. The frequency of upper respiratory infections before the epistaxis started has been investigated in several studies (table 1). The great variation of frequency in these studies – between one and a hundred per cent – depends most likely on the principle of selection of the patients and the use of different definitions of upper respiratory infection.

Acetylsalicylic acid. Tucker (1963) is the only author who has reported about the correlation between intake of acetylsalicylic acid and epistaxis. He noted that 4 per cent of the patients had taken acetylsalicylic acid before the bleeding started but regarded this to be coincidental.

In contrast to this, Parry and Wood (1967) discovered that 33 per cent of a control group (patients who visited a hospital due to other diseases than gastro-intestinal haemorrhage) had taken acetylsalicylic acid the week prior to the visit to the hospital.

Hypertension. The association between hypertension and epistaxis was investigated in different studies (Woodruff 1949, Hallberg 195 , Hara 196 , Pierce and Chasin 1962, Tucker 1963, Grabowski 1965, Serafini 1965, Philip and von Harder 1966, Popel 1969). It is difficult to draw conclusions from the results of these studies as neither control groups are studied nor definitions of hypertension are given.

In two studies (Mitchell 1959 and Shaheen 1970) the blood pressure in the patients with epistaxis was compared with the blood pressure of subjects in control groups. Mitchell found that the diastolic blood pressure was significantly higher in patients who had epistaxis (with no other nasal disease) than in the control group. The blood pressure was, however, not recorded in ..5 per cent of the patients. In contrast to this Shaheen did not find any difference in blood pressure between his patients and a control group.

In the Health Examination Survey of adults 1960–62 (USA), the blood pressure was measured in 6 672 subjects. When the prevalence of different blood pressures was compared with the occurence of epistaxis no correlation was found between subjects with low and high blood pressure and histories of epistaxis (Weiss 1972).

Hematological diseases. In textbooks of hematology (for instance Videbæk 1965) it is said that diseases with defects in the hemostasis and malignant hematopoetic tumours often have epistaxis as a leading symptom.

When patients with epistaxis have been examined malignant hematopoetic tumours have been reported in one to four per cent and defects in the hemostasis in one to a hundred per cent of the examined patients (table 1). In those studies where the patients were extensively examined with several tests (Laeber and Heinrich 1960, Maurer and Rühl 1965) more defects in the hemostasis were found.

C. Localisation of the bleeding source

Although the age of the patient is of importance for the localisation of the bleeding source many results are presented without regard to the age distribution of the patients.

In only one study on 136 hospitalized patients (Ogura and Senturia 1949) was the age distribution presented. All patients less than 15 years old had bleedings from the anterior part of the septum and 60 per cent of the patients more than 40 years of age had bleedings from posterior and lateral parts of the nasal cavity.

Hallberg (195) studied hospitalized patients with severe epistaxis. In 27 per cent of the patients the bleeding source was localized in the Kiesselbach area and in 17 per cent in other parts of the septum. The bleeding source was seen in other visible parts of the nasal cavity in 33 per cent and was invisible in 23 per cent of the patients.

In out-patients examined by Tucker (1963) 74 per cent of the patients had bleedings from septum, 10 per cent bled from other visible parts of the nose and in 16 per cent of the patients the bleeding source was not visible.

D Treatment of epistaxis

In ancient times epistaxis was treated in several different ways for example with gauze tampons and cauterisation In ancient Egypt both nasal cavities were completely filled with gauze when the patients had epistaxis (Kassel 1911) By local pressure to a visible or unvisible vessel the bleeding was arrested Various cauterizing agents were used *in ancient Greece and Rome* for example acetum, gallotanic acid antimony and soda (Kassel 1913) The drugs were in different ways introduced into the bleeding nasal cavity and part of the nasal mucosa was in this way destroyed Modifications of both these methods have been in use since then

1 Local treatment

a *Bleeding vessel or area visible.* Nowadays cauterisation is performed with chemicals like silver nitrate trichlor acetic acid or chromic acid or with electrical cauterization (Woodruff 1949 Ogura and Senturia 1949 Hallberg 1952 Hara 1962 Tucker 1963 Stecker and Lake 1965 Call 1969) and only the bleeding area or vessel is destroyed

A refined method of cauterization was described by Ringenberg (1963) With the aid of an operating microscope the bleeding vessel was identified the blood from the vessel was eliminated by suction and *the vessel destroyed by electrical* cauterization

Submucosal injections below the bleeding area have been performed with 3% water soluble Phlebocid® (Wodak 1966) The submucosal injection helped to arrest the bleeding by local pressure and Phlebocid gave an inflammatory reaction in *the mucosa with thrombophlebitis in the vessels.*

Submucosal injections with adrenalin 1 1 000 which give a vasoconstriction have been used by Kocsard Varo (1967) Adrenalin and other vasoconstrictor drugs are used for routine purpose on the mucosa surface

Frable (1968) sprayed a thin layer of plastic over the bleeding area *The bleeding was arrested* by local pressure without damage of the mucosa

The absorbable hemostatic sponge Spongostan® (Mayer 1952) and Surgicel® (Tibbels 1963) can be used when the bleeding is profuse Spongostan® and Surgicel® are preformed networks in which blood clotting is facilitated

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Defects in the vessels of the nasal mucosa can be treated with skin transplants (Saunders 1964) *Parts of the nasal mucosa are replaced with skin* The treatment is used in patients with hereditary hemorrhagic telangiectasia (Mb Osler) and septal perforations.

b *Bleeding vessel or area invisible* Usually anterior or posterior tampons of gauze or cotton have been used to treat invisible bleedings. Stevens (1951) and Bavon (1965) used a rectangular shaped balloon filled with water instead of an anterior gauze tampon The filled balloon arrested the bleeding by local pressure

A Foley balloon catheter was used instead of post nasal packing with tampons by Rege et al (1964) Fenn (1968) Brunnel (1968) and Barton *and Ray (1970) The inflated balloon* which filled up the entire epipharyngeal space prevented posterior bleedings by local pressure

Intranasal freezing with a Steven s balloon have been performed by Bluestone and Nixon (1970) and Hill and Jaccewics (1971) After freezing at −20°C for one hour a severe inflammatory reaction *was observed in the nasal mucosa* with thrombophlebitis in the vessels. Many medium sized vessels were permanently damaged

A severe inflammatory reaction in the nasal mucosa with thrombophlebitis in nasal vessels can also be produced by treatment with radiotherapy (Stewart and Sammon 1954 Salomon and Buch *Rasmussen 1965 Lord and Durden Smith 1971)* In the investigations mentioned 1 500 to 3 000 r were given on both nasal cavitites.

An injection of 2 per cent Lidocain® into fossa pterygopalatinae has been described as successful in severe posterior bleedings (Padmos 1968) Lidocain® gave a vasoconstriction of the spheno *palatine artery* and was reported *to arrest the* bleeding in 10 cases out of 11

As a rule arterial ligation of the external carotid artery or its branches or of the anterior ethmoidal artery has been successful when other local treatments have failed (Weddel et al 1945 MacBeth 1948 Hunter and Gibson 1969 Shaheen 1970)

The blood flow to the bleeding area decreased after the ligation and the bleeding was arrested in most cases

2. General treatment

It is a well known clinical observation that epistaxis sometimes is arrested when the patient is treated with tranquilizing drugs. Hypnosis was valuable in one case with recurrent nose bleedings (MacCord 1968).

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A patient who has a hematological disease with generalized defects in the hemostasis must be treated with drugs or transfusions in a suitable way (Morel and Belleville 1967)

Oestrogen hormones are described as suitable therapy in patients with repeated epistaxis as for example patients with Mb Osler (Jacobsen 1964 Harrison 1964). In what way the nose bleedings are arrested and prevented is not sufficiently investigated

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E. Vascular anatomy of the nasal mucosa – a short review

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According to these studies we now have rather good knowledge about the vascular architecture in the nasal cavity

Arteries. The *internal carotid artery* furnishes through the ophthalmic artery the anterior and posterior ethmoidal arteries (figure 1 and)

In man the anterior ethmoidal artery normally is much the larger and supplies the anterior third of the lateral wall of the nasal cavity and a similar portion of the septum.

The posterior ethmoidal artery is limited in its distribution to the region of the superior concha and the corresponding portion of the septum

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The sphenopalatine artery supplies the posterior and lower parts of the lateral wall and the septum. It has three branches which take a course partly in bony canals, partly in the periosteal layer of the nasal mucoperiosteum (Burnham 1935)

Proximal branches of the greater palatine artery furnish the lower posterior portion of the nasal fossa. Distal branches from the same artery supply a portion of the floor of the anterior part of the nasal fossa. The superior labial branch of the facial artery is distributed to the anterior part of the septum.

All arteries communicate frequently with one another. On the anterior portion of the septal cartilage the anastomoses are situated superficially in the mucosa. This site is known as Kiesselbach's area

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Figure 1 Arteries of the lateral nasal wall

Figure 2 Arteries of the nasal septum.

arteries contribute very little to the arterial vasculature of the nose. On the basis of intravital dye studies he also showed that the intranasal anastomoses, which link the two main arterial systems, are capable of accommodating a rapid and substantial migration of blood. This is what happens when the pressure in one of the systems is lowered after for instance ligation of the external or internal carotid artery or their branches.

Veins. The venous blood from the nasal mucosa passes to the external nasal plexus, the nasolacrimal plexus, anterior and posterior ethmoidal veins, veins behind and above the palate veins in the lateral part of the epipharynx, the sphenopalatine vein and the sphenoidal venous plexus.

Microvascular architecture. Our knowledge of the microvascular architecture in different parts of the nasal mucosa is based mainly on works by Burnham (1935) Swindle (1935) Messerklinger (1958) and Naumann (1961). A sketch with the proposed function of the minute vessels of the nasal mucosa based on other studies has been presented by Ingelstedt and Rundkrantz (1964) (figure 3)

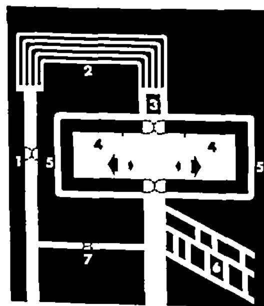


Figure 3 Sketch of the minute vessels of the nasal mucosa. 1 Arteriole. 2 Capillary network. 3 and 5 Postcapillary venules. 4 Sinusoid range of possible expansion of filled sinusoid. 6 Deep venous plexus. 7 Arteriovenous anastomosis. (Ingelstedt & Rundcrantz 1964)

The small arteries either communicate with small veins through arterio-venous anastomoses or with capillary networks. Three different capillary networks are described one in the periosteal layer another supplies the glands in the mucosa and the third in the subepithelial layer These networks are connected with one another and may empty either in venous plexuses or in sinusoidal spaces in the erectile tissue draining to deep intraosseous plexuses of veins. The venous plexuses give place to veins which increase in size but decrease in number and accompany the arteries.

The venous pathways in the turbinate areas differ from those in other parts of the nasal mucosa. In the mucosa of the inferior and middle turbinate and in some parts of the septum sinusoidal spaces with frequent intercommunications are situated. In the walls of these sinusoides are sphincters with ability to vary the calibre of the space within wide limits.

Innervation. The vessels of the nasal mucosa are innervated through autonomic sympathetic fibers which are vasoconstrictors and autonomic parasympathetic fibers which are vasodilatators (Larsell and Fenton 1936 Messerklinger 1958).

The vasomotor reactions of the vascular bed are also affected by vasoactive drugs for example adrenalin and acetylcholin (Naumann 1961).

Vascular bed reactions. The vascular bed in general reacts in a similar way on different traumatic agents (Brånemark 1968). The first sign of damage to the vascular bed is a slow circulation of blood corpuscles first seen in small veins This is followed by adhesion to the vessel wall of erythrocytes, platelets and leucocytes. Later on there is stasis in the vessels and development of microthrombi consisting of a fibrin network and blood corpuscles. The microthrombi might be washed away or they may completely block the vessels causing damage to the surrounding tissue

Naumann (1961) has shown that the vascular bed in the nasal mucosa reacts in the same way as described. From intravital microscopic observations on the nasal membranes of rabbits he has noted that mechanical stimulation gave a constriction of capillaries and veins with slow corpuscular circulation and sometimes stasis and white emboli. The arteries were usually only slightly constricted.

In man Naumann had the clinical experience that small mechanical stimulations only slightly

Figure 1 Arteries of the lateral nasal wall.

Figure 2. Arteries of the nasal septum.

CHAPTER 2

CLINICAL MATERIAL

Study groups

In this investigation subjects in a randomly selected population sample and patients who visited an ENT doctor due to epistaxis were studied. The subjects and patients were both asked questions in a questionnaire (chapter 3 A).

A. Population sample (P)

By the aid of a computer 439 inhabitants in the city of Goteborg were selected at random from the census register containing 450 000 subjects. In the ages under 60 years about every thirteen hundredth man and woman was selected. The selected subjects were divided into six groups with regard to sex and age. In the ages over 60 years about every seven hundredth man and woman was selected and divided into two groups with regard to sex. The reason why more subjects over 60 years of age were selected was a desire to get about an equal number of subjects in each group (table 2).

To selected subjects a questionnaire (chapter 3 A) was sent one of the four weeks 48, 49, 50 (1971) or 4 (1972). Those who did not return the questionnaires which were sent out the first three weeks were questioned by telephone the fourth week.

Answers were received from 410 subjects (93 %). Of those who answered 9 per cent were questioned by telephone. In all questionnaires all questions were answered. Those who did not answer were equally distributed in the groups (table 2).

B. Registered patients (R)

Before this study started questionnaires (chapter 3 A) were sent to all ENT-doctors (about 40) in the city of Goteborg. The doctors were told to ask some questions to all patients with epistaxis who visited the different practices or the hospital during the period from 1 July 1970 to 31 December 1971. The medical assistants were told to hand over a questionnaire to the doctor every time a

Within th[illegible] date the questionnaires were distributed [illegible]t random.

Table 2. Number of subjects and patients in the different study groups

	Men age group					Women age group					
	<20	20–39	40–59	≥60	total men	<20	20–39	40–59	≥60	total women	In all
Population sample											
Number of subjects who											
Answered	42	51	48	49	190	42	54	56	68	220	410
Did not answer to the questionnaire	3	3	4	4	13	4	6	1	5	16	29
Registered patients	144	127	179	202	662	102	64	92	208	466	1118
Hospitalized patients	1	9	34	28	72	1	9	8	21	39	111
Out patients	143	118	145	174	580	101	55	84	187	427	1007
[illegible] examined patients	2	13	39	46	100	3	11	14	27	55	155

and reversibly affected the vascular bed He assumed however that the same stimulation in an *inflammatory nasal mucosa* gave a more severe vascular bed reaction

When an inflammatory reaction *was induced in the nasal mucosa of rabbit (Naumann 1961) for* example by application of a drop of mustard oil a miximal vasodilatation and rapid blood flow was primary observed in *all vessels After about* 30 minutes no dilatation was seen and the blood flow was normal again Later on slowly moving leucocytes *were noted along the vessel walls* leucocyte diapedesis was also observed When the induced reaction was severe white emboli fibrin networks and finally fibrin-platelet plugs were formed in the vessels There was also noted increasing injuries in the vessel walls.

F Physiology of hemostasis – a short review

The physiology of hemostasis has been extensively *studied during the last century During this period* numerous investigations have also been published about different defects in the hemostasis In this *short review* is presented some basic facts available in text books of hemostasis (Nilsson 1971 Biggs 1972)

Hemostasis includes all mechanisms involved in arresting the bleeding. It is composed of four components vessel wall reaction platelet aggregation coagulation and fibrinolysis (figure 4)

Vessel wall reaction ⟶ *vasoconstriction*
Platelet aggregation ⟶ platelet plug formation
Coagulation ⟶ fibrin clot
Fibrinolysis ⟶ break down of fibrin

Figure 4 Schema of the hemostasis

Vessel wall reaction. When a vessel is damaged a vasoconstriction of short duration is initiated by a neurogenic or humoral mechanism. This reaction is of great hemostatic importance after injuries of *both arteries and veins. During the vasoconstriction the formation of a platelet plug starts*

Platelet aggregation. When the vessel is injuried the endothelial cells are damaged and the *subendothelial collagen denuded Platelets progressively* adhere to the collagen The aggregated platelets release factors which aggregate new platelets and *finally a platelet plug is formed This is called* primary hemostasis.

Coagulation. After a while fibrin threads appear in the platelet plug and form a weak network The fibrin originates from fibrinogen circulating in the blood The fibrinogen is converted to fibrin by the enzyme thrombin which in turn is formed from prothrombin activated by different coagulation factors. The thrombin also aggregates platelets and the platelets in turn release factors that activate prothrombin In this way both the platelet aggregation and the development of fibrin is accelerated Finally a dense network of fibrin platelets and erythrocytes, a blood clot has been formed

Fibrinolysis is an enzymatic break down of the fibrin network in the clot by means of plasmin The inactive plasminogen circulates in the blood and is incorporated in the clot Different activators for example blood activator tissue activator and the bacterial toxins *streptokinase and staphylokinase* can activate plasminogen The split products formed when the fibrin is digested act as inhibitors of the platelet *aggregation and the polymerisation* of fibrin threads. In this way this stage of the *hemostatic processes come to a steady state*

CHAPTER 2

CLINICAL MATERIAL

Study groups

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Registered patients	144	127	179	202	652	102	64	9	208	466	1118
Hospitalized patients	1	9	34	28	7[illegible]	1	9	8	1	39	111
Out patients	143	118	145	174	580	101	55	84	15[illegible]	42[illegible]	100
Extensively examined patients	2	13	39	46	100	3	11	14	[illegible]	5	15

patient with epistaxis was examined During the period 1 118 patients with epistaxis were registered, 88 per cent were registered at the hospital and 12 per cent at different practices outside the hospital

Most of the patients came directly to the hospital even if the way was shorter to an ENT-doctor outside the hospital In the afternoons and nights and on week-ends and holidays all patients with epistaxis had to visit the hospital because all practices outside the hospital were closed

The number of patients who were registered during different months is shown in figure 5 The number of patients in different sex and age groups is presented in table 2

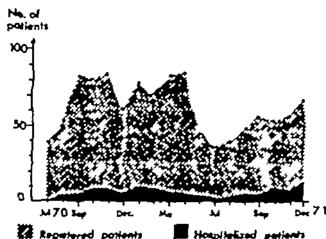


Figure 5. The number of patients who were registered and hospitalized during different months.

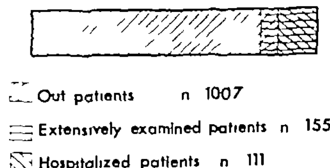


Figure 6. The different study groups of the registered patients.

The group of registered patients is composed of out patients and hospitalized patients (figure 6)

Hospitalized patients (H) During the registration period 111 of the registered patients were hospitalized due to epistaxis They were divided into eight groups with regard to sex and age (table ?)

Out patients (O). The 1 0007 out patients were divided into different sex and age groups (table 2)

Extensively examined patients (E) This group of patients constitutes the 111 hospitalized patients and 44 out patients selected at random from patients who came to the out patient department of the hospital between 9 and 12 a.m any of the days Monday to Thusday Age and sex distribution of these 155 patients is presented in table 2.

Blood pressure was recorded and samples from the nose and throat for bacterial isolation were taken in the patients when they were examined for the first time

Blood samplings for routine tests (chapter 3 F) serological tests (chapter 3 G) and routine tests of hemostasis (chapter 3 H) were performed at different lenghts of time after the first examination The samplings were carried out immediately the patients came to the hospital in 74 patients within 24 hours after the hospitalisation in 49 patients and after more than 24 hours hospitalisation in 3? patients.

During hospitalisation blood pressure hemoglobin concentration and reticulocyte counting were carried out repeatedly In out patients these tests were performed a second time two to four days after the first examination.

All patients were finally examined 17±10 days (range 8–42 days) after the first blood samplings were taken. On this occasion the blood pressure was recorded samples from the nose and throat taken for bacterial isolation blood samplings taken for determination of hemoglobin concentration erythrocyte sedimentation rate leucocyte count reticulocyte count serological tests and the routine tests of hemostasis fibrinogen APTT blood clotting factor VIII and II + VII + X The tests of capillary fragility bleeding time and platelet count were only performed in those patients who had an abnormal value on the first test occasion.

Subgroups. Some of the extensively examined patients who came to the hospital during the autumn 1971 were at random selected for the investigations of fibrinolytic activities of blood and nasal mucosa (chapter 4 I and 4 K) and histological examination of the nasal mucosa (chapter 4 D) These patients are presented individually in the separate chapters.

CHAPTER 3

METHODS

A. The questionnaires

The subjects in the population sample (P), the out patients (O), the hospitalized patients (H) and the extensively examined patients (E) were asked the following questions.

1. Has any doctor at any time found that you have had high blood pressure? yes – no (POH)
2. Do you regularly take drugs as treatment for high blood pressure? yes – no (PH)
3. Have you at any time during the last seven days taken any drugs as treatment for headache, aches, or pains? (the names of eight of the most common drugs containing acetylsalicylic acid were mentioned) yes – no (POH)
4. Have you at any time during the last seven days had a common cold, caught, sore throat or fever? yes – no (POH)
5. Have you any time consulted a doctor and been treated for nose bleeding? yes no (P)
6. Have you had any nose bleeding the last seven days? (yes – no (P)
7. How often do you bleed from the nose
   a. Never had any bleeding (P)
   b. First time in life (OH)
   c. Have had single bleedings before (POH)
   d. Have had single bleedings every year (POH)
   e. Have had several bleedings every year (POH)
8. Do you use to bleed from the nose when you have a common cold? yes – no (P)
9. Do you use to bleed from the nose when you are tired and/or busy and/or stressed? yes – no (P)
10. Did the bleeding start (OH)
    a. When you blew your nose?
    b. When you sneezed?
    c. After picking the nose?
    d. After a blow against the nose?
    e. After puncture of sinus owing to sinusitis?
    f. After physical exhaustion?
    g. After psychical exhaustion?
    h. Without any obvious reason?
11. Do you have any near relatives who use to bleed from the nose frequently? Parents yes – no Children yes – no Brothers or sisters yes – no (E)
12. Do you use to get hematomas on the arms (yes – no) or on the body (yes – no) without traumas? (E)
13. Do you use to bleed for a long time after a tooth extraction (yes – no) or after slight skin cuts (yes – no)? (E)

B. Clinical examination

After the clinical examination of the patients the examinating doctor classified the localisation of the bleeding source and the kind of bleeding. The bleeding might come from 1. Kiesselbach area 2. Other visible parts of the septum 3. Visible lateral parts and floor of the nose 4. Invisible localisation.

When the kind of bleeding was noted the following five groups were used 1. Distinct arterial bleeding 2. Distinct venous bleeding 3. Profuse bleeding 4. Kind of bleeding impossible to classify 5. No bleeding when examined.

C. Principles of treatment

The principles of treatment were to arrest the bleeding with as little damage to the nasal mucosa as possible.

When the patient called the doctor by telephone, the patient was told to blow the nose to get rid of old blood clots in the nose. He was also

told to sit up breath through the mouth and press *the nares together between the thumb and fore* finger for 10 minutes.

If the bleeding in spite of this continued the *patient was told to blow the* nose once again then put up a large *piece of cotton soaked with* paraffin (if available) in the nose and apply the *finger grip for another 10* minutes.

If the nose bleeding continued the patient was instructed to visit the doctor

Before the examination the patient was told to blow this nose remaining clots were evacuated with suction and the bleeding source localized. The main lines of the doctors local treatment were as follow

Visible bleeding source. A piece of cotton soaked with local anesthesia and a vasoconstrictor was put into the bleeding nasal cavity if the bleeding source was *distinct* and visible on the septum. The cotton was taken away after the bleeding was arrested. As small area of the mucosa as possible was then cauterized by touching with *solid cromic acid on a small steel wire for a* second. The excess of acid was washed away with saline not sodium hydroxide which destroys the surrounding mucosa (Brånemark 1974) Electrical cautery was used in visible severe arterial bleedings.

A visible *profuse* bleeding on the septum or lateral parts or the floor of the nose was treated in a new way with a gelatine sponge (Spongostan®) which has a hemostatic effect soaked with a 10 per cent solution of tranexamic acid (Cyklokapron®) which has an antifibrinolytic effect. The soaked Spongostan® was placed against the bleeding area. Sometimes invisible small bleedings were treated in this way too. Most of the bleedings treated with Spongostan® and Cyklokapron® were bleedings which, before this investigation *started, were treated with anterior gauze tampons.* The Spongostan® disappeared by itself without any complications within two or three days in forward or backward direction.

Invisible bleeding source. When the bleeding source could be suspected to be localized in anterior and/or superior parts *of the nasal cavity* the patient was treated with gauze tampons after local anesthesia had been sprayed on the nasal mucosa. The tampons were packed into the nose until they filled up the anterior and/or superior parts of the bleeding nasal cavity and arrested the *bleeding by local pressure*

In bleedings localized in posterior parts of the nose both a posterior Foley catheter tampon (nr *14) and anterior gauze tampons were used. The tip of the catheter outside the balloon, was first* cut. The balloon of the catheter which then was *placed in* epipharynx and filled with about 10 ml saline, occluded the posterior parts of the nose and prevented the anterior gauze tampons disappearing down the throat. The whole bleeding nasal cavity was packed with anterior gauze tampons. Finally the catheter was fixed forward with a plastic tube clamp. The external naris was protected against pressure injuries by a cut eye pad below the clamp.

All patients who were treated with posterior and anterior tampons were hospitalized as well as some of the patients who were treated with anterior tampons. Schema for removement of the tampons is described in chapter 4 I.

In all patients the therapy was regarded as successful if no new bleeding which required new *local treatment* occured *within 24 hours after the* patient had left the examining doctor

D Blood pressure

The blood pressure was measured according to *Rose and Blackburn (1968) with a sphygmomanometer* attached to a 13 cm wide and 26 5 cm long cuff on the right over arm. The readings were *made after 4–5 minutes rest with attached cuff in* a sitting position with the right arm placed horisontally on a table The cuff was rapidly *inflated to a level above the radial palpatory* pressure and then deflated. The systolic pressure was determined when the sound of the brachial *artery was heard in the stethoscope (phase I) and* the diastolic pressure when no sound was heard (phase V).

All readings, except part of the first ones, were made between 9 and 12 a.m. by the author Of various readings in the same patient the pressure recorded at the final examination, was used in this investigation.

E Bacterial isolation

The first samples for bacterial isolation were always taken from the nose and throat before the patients were treated. *One sample was taken by*

the aid of a nose speculum from the posterior parts of the middle meatus on the side opposite to the bleeding. Another sample was taken from the throat.

The second samples were taken in the same way 17±10 days (range 8–42 days) after the first.

All bacterial isolations were performed at the Bacteriological Department of the hospital. All bacterial strains of beta-hemolytic streptococci and staphylococcus aureus which were found were frozen and kept for later determination of the fibrinolytic activity (chapter 3.1).

F. Routine tests

The following tests were performed at the Central Chemical Department of the hospital using standard methods. The reference values stated by the Department are presented.

I. Hemoglobin concentration (standardized with hemoglobin-cyanide standard, Merck) reference value
men 13.2–16.6 g/100 ml
women 11.6–14.9 g/100 ml

II. Erythrocyte sedimentation rate reference value
men ≤ 20 mm/hr
women ≤ 28 mm/hr

III. Leucocyte count (microscopic counting) reference value 3 500–9 000 leucocytes/mikroliter

IV. Reticulocyte count (microscopic counting) reference value 0.2–1.0 percentage of total erythrocytes

V. Creatinine concent ation in serum
reference value men 0.7–1.3 mg/100 ml
women 0.6–1.2 mg/100 ml

VI. Transaminases in serum. Aspartate aminotransferase (ASAT or GOT) and alanine aminotransferase (ALAT or GPT) were determined by kinetic technique using commercial reagents (Boehringer Mannheim, catalogue numbers 15957 and 15958) at an incubation temperature of 30°C
reference value
7 U/l
7 U/l

G. Serological tests

Blood samples for serological tests were analysed at the Bacteriological Department of the hospital. The reference values stated by the Department are presented.

I. Antistreptolysine titer (AST) reference value: a difference of two titer steps or more between the two test occasions or a single test value of more than 400 U/ml.

II. Antistaphylolysine titer (ASTA) reference value: a difference of two titer steps or more between the two test occasions or a single test value of more than 4 U/ml.

III. C-reactive protein (CRP) was determined according to Nilsson (1968) reference value less than 5 μg/ml

H. Routine tests of hemostasis

Tests of vessel and platelet functions and blood clotting were performed at the Coagulation Laboratory of the hospital. The reference values and abnormal values indicating defects in the hemostasis stated by the Laboratory are presented.

I. Capillary fragility. Two methods were used, 123 patients were tested with the stasis method and 12 patients with the suction method.

The stasis method: a 13 cm wide and 26.5 cm long cuff was placed around the left overarm and inflated to 70 mm Hg for 5 minutes. Abnormal value: more than 15 petechiae within a circle with 5 cm diameter on the forearm 2 minutes after the cuff was deflated.

The suction method: a suction cup of 1 cm diameter was placed on the back of the shoulder and a negative pressure of 20 mm Hg applied for 1 minute.

Abnormal value: more than 7 petechiae in the suction area 2 minutes after the cup was taken away.

II. Bleeding time. Two methods were used, 126 patients were tested with Dukes method and 12 patients with a modification of Ivys method.

Abnormal values:
≥ 4 minutes with Dukes method
≥ 11 minutes with Ivys method

told to sit up, breath through the mouth and press the nares together between the thumb and fore finger for 10 minutes.

If the bleeding in spite of this continued the patient was told to blow the nose once again then put up a large piece of cotton soaked with paraffin (if available) in the nose and apply the *finger grip for another 10 minutes.*

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All patients who were treated with posterior and anterior tampons were hospitalized as well as some of the patients who were treated with anterior tampons. Schema for removement of the tampons is described in chapter 4 L.

In all patients the therapy was regarded as successful if no new bleeding which required new local treatment occured within 24 hours after the *patient had left the examining doctor*

D Blood pressure

The blood pressure was measured according *to* Rose and Blackburn (1968) with a sphygmomanometer attached to a 13 cm wide and 26.5 cm long cuff on the right over arm. The readings were made after 4—5 minutes rest with attached cuff in a sitting position with the right arm placed horizontally on a table. *The cuff was rapidly* inflated to a level above the radial palpatory pressure and then deflated. The systolic pressure was determined when the sound of the brachial artery was heard *in the stethoscope (phase I) and* the diastolic pressure when no sound was heard (phase V).

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E. Bacterial isolation

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+ = fibrinolytic activity demonstrable
++ = fibrinolytic activity less than reference strain H 64
+++ = fibrinolytic activity equal to the reference strain H 64
++++ fibrinolytic activity stronger than the reference strain H 64

K. A method for determination of fibrinolytic activity in euglobulin precipitate from blood plasma

The fibrinolytic activity in blood can be demonstrated by different methods. The most physiological method probably is the whole blood clot lysis time. Unfortunately this method is insensitive and can only be used when there is a markedly increased fibrinolytic activity. At low levels of fibrinolytic activity the lysis time is long and the end point reading difficult.

When low levels of fibrinolytic activity are studied it is more suitable to use the euglobulin precipitation method. The euglobulin fraction from plasma is after dilution precipitated at pH 5 to 6.4. Most of the fibrinolytic activity is found in the precipitate while most of the fibrinolytic inhibitors remain in the supernate (Kowalski et al 1959, Blix 1964, Ygge 1970).

The fibrinolytic activity in the euglobulin precipitate can be measured in two ways, either as euglobulin clot lysis time or by means of the fibrin plate method. When weak fibrinolytic activity is measured the lysis time is very long by the clot lysis time method and variations in fibrinogen concentrations in the euglobulin fraction interfere with the results (Ygge 1970).

The fibrin plate method which was introduced by Permin (1947, 1950) and Astrup et al (1950) has been improved by Astrup and Müllertz (1952) and Brakman (1967). This method is more sensitive to low levels of fibrinolytic activities than the lysis time method. When using the *fibrin plate* method the procedure can be standardized (Ygge 1970).

The fibrinolytic activity in blood, depends on released tissue activator from the endothelial cells (Astrup 1956, Fearnley 1965 and Nilsson et al 1970). The activity is increased after emotional stress, physical exertion, shock, injections of pyrogens and vasoactive drugs (Fearnley 1965).

After venous occlusion the fibrinolytic activity in the blood is increased due to release of tissue activator (Clarke et al 1960, Robertson et al 1971). According to Robertson, who has carried out systematic studies on venous occlusions of the arms and legs, the release of activator depends on the pressure in the occluding cuff and the time during which the cuff is inflated. The venous occlusion method probably is a measure of the fibrinolytic capacity of the venous wall.

The *collection of blood and euglobulin precipitation* have been carried out according to Ygge (1970). After precipitation at pH 6.4 the supernatant was discarded. The precipitate was dissolved in barbital buffer (chapter 3 L) to half the original plasma volume for 5 minutes and then diluted 3:4, 1:2, 3:8 and 1:4 with barbital buffer. The undiluted dissolved precipitate and the dilutions were then tested on fibrin plates.

Determination of fibrinolytic activity. The fibrin plate was prepared as described in chapter 3 L. The same pig heart standard of testing the fibrin plates was also used. 20 µl of each tested solution was placed on a fibrin plate with an Eppendorf automatic pipette. Each solution was tested on two or three plates. After 20 hours incubation at 37°C the lysis areas were measured as described in chapter 3 L. The mean values from the tested solutions were calculated.

Venous occlusion. The occlusion was produced by application of a sphygmomanometer cuff wrapped round the left over arm. The cuff was inflated for exactly 10 minutes to 110 mm Hg. The subject was lying down during the occlusion. Blood samples were obtained from an antecubital vein before application of the cuff and immediately before deflation of the latter. The blood was tested as previously described.

Methodological investigations

The slope of the dilution curves. In 45 patients the spontaneous fibrinolytic activity was studied on two different occasions. Dilution curves of the fibrinolytic activity were determined statistically as regression lines by the aid of a computer with degree of dilution on the abcissa and lysis area on the ordinate.

In order to investigate whether the slopes of the two dilution curves in one patient were approximately identical the following statistical test was performed.

III Platelet count. The platelets were counted in a celloscope (Ljungberg & Co Stockholm Sweden).
Reference value 150.000–450.000 platelets/mikroliter
Abnormal value less than 150.000 platelets/mikroliter

Blood clotting tests

IV Fibrinogen was determined in accordance with Morrison's syneresis method as modified by Blombäck (1958). To prevent lysis of fibrinogen during the analysis, lysine ethylester was added as described by Bergstrom et al (1960)
Reference value 0.2–0.4 g/100 ml
Abnormal value less than 0 2 g/100 ml

V Blood coagulation faktor II VII X was determined with the commercial reagent Simplastin A (General Diagnostic Division, Werner Lambert Morris Plains USA) according to Koran-Bengtsen (1970)
Reference value 70–130 per cent
Abnormal value less than 70 per cent

VI Activated partial thromboplastin time (APTT) was determined with the commercial reagent Platelin plus Activator (General Diagnostic Division, Warner Lambert, Morris Plains, USA.)
Reference value 35–45 seconds
Abnormal value more than 45 seconds

VII Blood coagulation factor VIII (antihemophilic factor A) was determined according to Hardisty and Mac Pherson (196?)
Reference value 50–150 per cent
Abnormal value less than 50 per cent

I. A method for determination of fibrinolytic activity in bacterial strains

In chapter 3 E is mentioned how bacterial strains were isolated. Freshly isolated strains of DNAse positive staphylococci (staphylococcus aureus) and group A hemolytic streptococci were grown in TY medium (Holm and Falsen 1967) for 16 hours at 37°C. The recultures were kept frozen at −20°C after addition of glycerol.

All bacterial strains were tested during springtime 1972. After thawing the strains were reinoculated in TY medium for 16 hours at 37°C. The bacterial growth was estimated by registration of the turbidity in the culture by using a Beckman C spectro photometer. The same turbidity was sought to attain in all cultures. The fibrinolytic activity was measured in the clear supernate after centrifugation of the culture at 1500 G for ?0 minutes.

For the preparation of *fibrin agar plates* the method of Holmstrom (1965) was employed. Fibrinogen of human origin* was diluted with tris buffer pH 7 5 to a final concentration of _ g/l (0 2 %) The human thrombin used was without detectable amount of plasminogen (Berg et al 1966) and contained 20 N I H units per ml. At +40°C 5 ml fibrinogen was mixed with 0 5 ml thrombin and 5 ml agar (? per cent in tris buffer pH 7 5)

The plate was prepared in a 10 cm plastic Petri dish. After gelifi ation five holes with 4 mm diameter were punched in each agar plate. Each basin held 0.017 ml.

Determination of fibrinolytic activity. The basins in the fibrin agar plates were filled with the supernates of the centrifuged cultures. The fibrin plates were inoculated at 37°C. The diameters of the lysis zones on the plates were then measured at different times of incubation. The final registration was based on the reading performed after ?0 hours incubation.

Reference bacterial strain. A wellknown streptokinase producing strain was used as reference bacterial strain (strain H 64 Lancefield group C). The fibrinolytic activity of the culture supernate from this strain was compared with the fibrinolytic activity of the culture supernates from the patient strains. The culture supernate of strain H 64 had a streptokinase activity of 00 units per ml.

Streptokinase reference. A streptokinase preparation (Kabikinas)* was also used as reference. The streptokinase preparation was used in different dilutions. The diameters of the lysis zones of these dilutions were compared with the lysis zones of the supernates from the cultures of the patient strains as well as the reference bacterial strain

Classification of the fibrinolytic activity. The fibrinolytic activity of the different patient bacterial strains was classified in five groups

O = no fibrinolytic activity observed

* Kindly supplied by AB KABI Stockholm, Swede

+ = fibrinolytic activity demonstrable
++ = fibrinolytic activity less than reference strain II 64
+++ fibrinolytic activity equal to the reference strain II 64
++++ fibrinolytic activity stronger than the reference strain II 64

K. A method for determination of fibrinolytic activity in euglobulin precipitate from blood plasma

The fibrinolytic activity in blood can be demonstrated by different methods. The most physiological method probably is the whole blood clot lysis time. Unfortunately this method is insensitive and can only be used when there is a markedly increased fibrinolytic activity. At low levels of fibrinolytic activity the lysis time is long and the end point reading difficult.

When low levels of fibrinolytic activity are studied it is more suitable to use the euglobulin precipitation method. The euglobulin fraction from plasma is after dilution precipitated at pH 5.2 to 6.4. Most of the fibrinolytic activity is found in the precipitate while most of the fibrinolytic inhibitors remain in the supernate (Kowalski et al 1959, Blix 1964, Ygge 1970).

The fibrinolytic activity in the euglobulin precipitate can be measured in two ways, either as euglobulin clot lysis time or by means of the fibrin plate method. When weak fibrinolytic activity is measured the lysis time is very long by the clot lysis time method and variations in fibrinogen concentrations in the euglobulin fraction interfere with the results (Ygge 1970).

The fibrin plate method which was introduced by Permin (1947, 1950) and Astrup et al (1950) has been improved by Astrup and Mullertz (1952) and Brakman (1967). This method is more sensitive to low levels of fibrinolytic activities than the lysis time method. When using the fibrin plate method the procedure can be standardized (Ygge 1970).

The fibrinolytic activity in blood, depends on released tissue activator from the endothelial cells (Astrup 1956, Fearnley 1965 and Nilsson et al 1970). The activity is increased after emotional stress, physical exertion, shock, injections of pyrogens and vasoactive drugs (Fearnley 1965).

After venous occlusion the fibrinolytic activity in the blood is increased due to release of tissue activator (Clarke et al 1960, Robertsson et al 1971). According to Robertsson, who has carried out systematic studies on venous occlusions of the arms and legs, the release of activator depends on the pressure in the occluding cuff and the time during which the cuff is inflated. The venous occlusion method probably is a measure of the fibrinolytic capacity of the venous wall.

The collection of blood and euglobulin precipitation have been carried out according to Ygge (1970). After precipitation at pH 6.4 the supernatant was discarded. The precipitate was dissolved in barbital buffer (chapter 3 L) to half the original plasma volume for 5 minutes and then diluted 3:4, 1:2, 3:8 and 1:4 with barbital buffer. The undiluted dissolved precipitate and the dilutions were then tested on fibrin plates.

Determination of fibrinolytic activity. The fibrin plate was prepared as described in chapter 3 L. The same pig heart standard of testing the fibrin plates was also used. 20 µl of each tested solution was placed on a fibrin plate with an Eppendorf automatic pipette. Each solution was tested on two or three plates. After 20 hours incubation at 37°C the lysis areas were measured as described in chapter 3 L. The mean values from the tested solutions were calculated.

Venous occlusion. The occlusion was produced by application of a sphygmomanometer cuff wrapped round the left over arm. The cuff was inflated for exactly 10 minutes to 110 mm Hg. The subject was lying down during the occlusion. Blood samples were obtained from an antecubital vein before application of the cuff and immediately before deflation of the latter. The blood was tested as previously described.

Methodological investigations

The slope of the dilution curves. In 45 patients the spontaneous fibrinolytic activity was studied on two different occasions. Dilution curves of the fibrinolytic activity were determined statistically as regression lines by the aid of a computer with degree of dilution on the abscissa and lysis area on the ordinate.

In order to investigate whether the slopes of the two dilution curves in one patient were approximately identical the following statistical test was performed.

III Platelet count. The platelets were counted in a celloscope (Ljungberg & Co Stockholm Sweden).
Reference value 150.000–450.000 platelets/mikroliter
Abnormal value less than 150.000 plateles/mikroliter

Blood clotting tests

IV Fibrinogen was determined in accordance with Morrison's syneresis method as modified by Blombäck (1958). To prevent lysis of fibrinogen during the analysis, lysine ethylester was added as described by Bergstrom et al (1960).
Reference value 0.2–0.4 g/100 ml
Abnormal value less than 0.2 g/100 ml

V Blood coagulation faktor II VII X was determined with the commercial reagent Simplastin A (General Diagnostic Division Werner Lambert, Morris Plains, USA) according to Korsan-Bengtsen (1970)
Reference value 70–130 per cent
Abnormal value less than 70 per cent

VI Activated partial thromboplastin time (APTT) was determined with the commercial reagent Platelin plus Activator (General Diagnostic Division, Warner Lambert, Morris Plains, USA.)
Reference value 35–45 seconds
Abnormal value more than 45 seconds

VII Blood coagulation factor VIII (antihemophilic factor A) was determined according to Hardisty and Mac Pherson (1962).
Reference value 50–150 per cent
Abnormal value less than 50 per cent

I. A method for determination of fibrinolytic activity in bacterial strains

In chapter 3 E is mentioned how bacterial strains were isolated. Freshly isolated strains of DNAse positive staphylococci (staphylococcus aureus) and group A hemolytic streptococci were grown in TY medium (Holm and Falsen 1967) for 16 hours at 37°C. The recultures were kept frozen at −20°C after addition of glycerol.

All bacterial strains were tested during spring time 1972. After thewing the strains were reinoculated in TY medium for 16 hours at 37°C. The bacterial growth was estimated by registration of the turbidity in the culture by using a Beckman C spectro photometer. The same turbidity was sought to attain in all cultures. The fibrinolytic activity was measured in the clear supernate after centrifugation of the culture at 1500 G for 20 minutes.

For the preparation of *fibrin agar plates* the method of Holmstrom (1965) was employed. Fibrinogen of human origin* was diluted with tris buffer pH 7.5 to a final concentration of 2 g/l (0.2 %). The human thrombin used was without detectable amount of plasminogen (Berg et al 1966) and contained 20 N I H units per ml. At +40°C 5 ml fibrinogen was mixed with 0.5 ml thrombin and 5 ml agar (2 per cent in tris buffer pH 7.5)

The plate was prepared in a 10 cm plastic Petri dish. After gelification five holes with 4 mm diameter were punched in each agar plate. Each basin held 0.017 ml.

Determination of fibrinolytic activity. The basins in the fibrin agar plates were filled with the supernates of the centrifuged cultures. The fibrin plates were inoculated at 37°C. The diameters of the lysis zones on the plates were then measured at different times of incubation. The final registration was based on the reading performed after 20 hours incubation.

Reference bacterial strain. A wellknown streptokinase producing strain was used as reference bacterial strain (strain H 64 Lancefield group C)* The fibrinolytic activity of the culture supernate from this strain was compared with the fibrinolytic activity of the culture supernates from the patient strains. The culture supernate of strain H 64 had a streptokinase activity of 200 units per ml.

Streptokinase reference. A streptokinase preparation (Kabikinas) was also used as reference. The streptokinase preparation was used in different dilutions. The diameters of the lysis zones of these dilutions were compared with the lysis zones of the supernates from the cultures of the patient strains as well as the reference bacterial strain.

Classification of the fibrinolytic activity. The fibrinolytic activity of the different patient bacterial strains was classified in five groups

O = no fibrinolytic activity observed

* Kindly supplied by AB KABI Stockholm, Sweden

3 mm). The nasal bleedings were treated by application of a piece of gelatine sponge (Spongostan®) soaked with tranexamic acid (Cyklokapron®). The tissue biopsies were stored at −20°C until analyzed.

Solutions (all the reagents were p.a.)

I. *Concentrated extraction solution*. In a flask 10.31 g sodium barbital and 194.36 g potassium thiocyanate were dissolved in 200 ml distilled water. 250 ml 0.1 M hydrochloric acid and 50 ml salt solution (pH = 8.35).

II. *Extraction solution*. Concentrated extraction solution was diluted with equal parts of distilled water.

III. *Salt solution*. In a 1000 ml volumetric flask 4.89 g calcium chloride dihydrate and 2.79 g magnesium chloride hexahydrate and 109.12 g sodium chloride were dissolved in distilled water and diluted to 1000 ml.

IV. *Acid solution*. In 10 ml 1 M hydrochloric acid was dissolved 1.944 g potassium thiocyanate. The solution was prepared daily.

V. *Potassium chloride solution pH 4.2*. To 24 parts 0.15 M potassium chloride solution one part 0.3 M potassium acetate buffer pH 4.2 was added. One part of this solution was neutralized by 0.4 parts of fibrin plate buffer.

VI. *Fibrin plate buffer*. In a 1000 ml volumetric flask 10.31 g sodium barbital was dissolved in 675 ml distilled water and 250 ml 0.1 M hydrochloric acid and 50 ml salt solution were added. The pH was adjusted to 7.75 with 0.1 M hydrochloric acid and the solution diluted to 1000 ml with distilled water.

VII. *Barbital buffer*. Prepared as fibrin plate buffer but without salt solution.

VIII. *Combustion acid*. In 80 ml concentrated sulphuric acid 18 g potassium sulfate, 0.8 g copper sulfate, 2.7 g mercury sulfate and 0.2 g selenium were dissolved by boiling for 4 hours.

IX. *Ninhydrin reagents*. In 12.5 ml ethylenglycol-mono-methyleter 0.05 g hydrindantin and 0.33 g ninhydrin were dissolved. To the solution 4.2 ml 4 M sodium acetate buffer pH 5.5 was added. The ninhydrin reagent solution was prepared daily.

Fibrinogen

Bovine fibrinogen was prepared according to Blombäck (1967) from citrated plasma. The fibrinogen was stored at −70°C in plastic tubes containing 10 to 25 ml fibrinogen solution in a concentration of 10.5 g fibrinogen per liter, a ionic strength of 0.30* and pH of 7.5.** When fibrin plates were made a tube was defrosted and used after dilution.

Thrombin

Human crude thrombin prepared according to Berg et al (1966) was purified by gel filtration and ion exchange chromatografy (Berg et al 1966). After the chromatografy the thrombin was diluted with distilled water to a concentration of 20 NIH units of thrombin per ml. In the purified thrombin no plasminogen was found (Berg et al 1966).

The procedure to make the fibrin plate

The fibrinogen was filtered through glass wool, diluted with distilled water to ionic strength 0.15 and with fibrin plate buffer to a final fibrinogen concentration of 2 g/liter (0.2 %). The fibrinogen was divided into portions of 3 ml each and mixed with 3 ml fibrin plate buffer and 0.25 ml thrombin solution. The mixture was poured into a Petri glass dish, with a diameter of 10 cm and allowed to clot for one hour. A final fibrinogen concentration of 1 g/liter (0.1 %) gave a firm and opalescent fibrin layer in which the lysis areas were easy to read.

Application of the tissue extract solutions

30 µl of each dilution (1:1, 1:2, 1:3, 1:4, 1:8) was placed on a fibrin plate by means of an Eppendorf automatic pipette. Each tissue extract dilution was tested on three or four different fibrin plates.

Measuring of the lysis areas

After 20 hours incubation at 37°C the lysis areas were measured by means of a microscope (magnitude 6,3 X) with a hair scale in one of the ocular lenses. Two diameters perpendicular to each other were measured and the product of these was taken as the surface area and expressed in mm² (Astrup and Mullertz 1952). Thus the area measured was

* adjusted with distilled water
** adjusted with sodium hydroxide

Let $\Delta + kE$ be the difference between the estimated slopes on occasion one and two in a patient selected at random It is assumed that Δ, the differen e between the exact slopes, is normally distributed with mean u and standard deviation w If the slopes are identical then $u = w = O$ k is a constant which depends on the number of observations on which the estimations are based. E is assumed to be a normally distributed random variable with mean O and standard deviation τ The random variables Δ and E are assumed to be independent.

With the above mentioned postulations, the hypotheses $u = O$ (*t test*) and $w = O$ (*F test*) were tested by use of the values from the patients. Both the hypotheses were accepted on the level $p < 0.05$ This does not mean that $u = O$ and $w = O$ but it means that u and w differ so little from O (compared with τ), that each pair of dilution curves can as a good approximation be regarded as parallel

In 12 patients the dilution curves before and after venous occlusion were tested in the same way The slopes of these dilution curves could also as a good approximation be regarded as parallel

With these tests it has been justified that it is possible to compare dilution curves of one patient.

The presented value of the fibrinolytic activity

On the dilution curves the fibrinolytic activity of dilution 1 2 was determined statistically and compared with the mean values of the measured lysis areas of dilution 1 2. The coefficient of variation between these values was 8 per cent.

The statistically determined lysis areas of dilution 1 2 were presented as the fibrinolytic activity in euglobulin precipitate from plasma.

L. A micro method for determination of tissue plasminogen activator in human nasal mucosa

The concentration of plasminogen activator in human tissues varies individually and in different tissues. A high concentration has been found in uterus, adrenals, lymph nodes, prostate and thyroid. Little or no activity at all has been noted in testes, spleen and liver (Albrechtssen 1959 Fearnley 1965 Astrup 1966).

The plasminogen activator can be extracted from the tissue It has been shown to be more or less soluble in different solutions such as saline (Macfarlane and Bigg 1948, Astrup and Sterndorff 1956 Albrechtssen 1958) potassium acetate buffers at pH 4 2 (Bachman et al 1964) and potassium thiocyanate (Astrup and Stage 1957).

In 1957 Astrup and Albrechtssen described a method for quantitative determination of acid stable plasminogen activator in tissue. This method is still widely used for determination of tissue activator Large pieces of tissue are however, required and the extraction procedure takes about six hours.

Todd described 1959 a histochemical semiquantitative method for determination of plasminogen activator This method has since then been used by several other investigators (Kwaan and Astrup 1964 Pandolfi et al 1967 Pettersson 1968 etc) By Todd s method it has been found that plasminogen activators are localized in the endothelial cells in the capillaries and the small veins.

A comparison between Todd s method and the present method by use of biopsies from human carcinomatosis (Petterson et al 1973) showed a good correlation.

Nasal mucosa is suitable for tissue plasminogen activator studies because it is easy to take biopsies from the tissue which is very rich in capillaries and small veins (Batson 1954).

Studies of tissue plasminogen activator in nasal mucosa have previously been carried out by use of saline extraction (Sasaki et al 1959) and potassium thiocyanate extraction (Buch Rasmussen 1966). In none of these studies has the plasminogen activator been determined quantitatively

The purpose of this investigation was to work out a quantitative method for determination of tissue plasminogen activator in small pieces of human nasal mucosa (3–5 mg).

Material and methods

Tissues

1 Postmortal nasal mucosa was obtained from eight bodies. The inferior concha on one or both sides were removed within three hours after death The nasal mucosa was divided into small pieces, which were stored at – 0°C

2 On living subjects 3–5 mg nasal mucosa biopsies were taken without anesthesia from the inferior concha by a Hartman ear polyp forceps (O

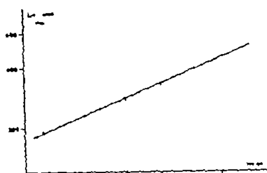


Figure 7 Standard curve On two different occasions, frozen supernatants from three different tubes of lyophilized pig heart standard were diluted with extraction solution. On the first occasion each dilution was tested on three different fibrin plates and on the second occasion on six different fibrin plates. A total of 27 incubations were made with each dilution (1:1, 1:2, 1:3, 1:4 and 1:8). The mean values from each of these 27 incubations were calculated and a standard curve was drawn on double logarithmic paper with degree of dilution on the abscissa and the lysis areas in mm² on the ordinate. On the abscissa was also plotted the amount of pig heart units (PHU) per ml.

The standard curve was also statistically estimated as regression line according to the least square method Y = 374 – 274X. The correlation coefficient between dilution and lysis area was 0.99.

Dilution	Lysis area mm² (mean value of 27 determinations)	± S.D.	Variation coefficient (± S.D. in per cent)
1:1	439	40	9 %
1:2	323	22	%
1:3	274	24	9 %
1:4	251	27	11 %
1:8	193	23	12 %

lysis area given by one mg lyophilized pig heart standard.

The standard curve

The construction of the standard curve is described in figure 7. It was used as long as the same fibrinogen preparation was used. Each day the standard curve was checked with pig heart standard supernatant. If the mean value of six incubations was within the limit 441 48 mm² the standard curve was accepted.

The pig heart standard supernatant was tested against urokinase (Leo Pharmaceutical Products, Denmark.) With the fibrinogen used in the experiments 6.3 PHU gave the same lysis area on the fibrin plates as 2 Ploug units of urokinase. (Three different tubes with 2.400 Ploug units of urokinase were diluted with fibrin plate buffer to 2 Ploug units of urokinase per ml. The mean value of six incubations from each dilution was calculated.)

Method for determination of tissue plasminogen activator

Total activity

The nasal mucosa was weighed and 0.5 ml distilled water per mg of tissue added. Homogenisation was carried out in a Potter glass homogenisator at +4°C for 4 minutes at a speed of 500 rpm. Two samples containing 100 µl each were then taken for nitrogen determination. To the rest of the suspension an equal part of concentrated extraction solution was added. The suspension was homogenised for a further one minute and then centrifuged at +4°C for 20 minutes at 1700 G. The sediment was discharged and the supernatant was divided into two portions. One of the portions was diluted with extraction solution (1:1, 1:2, 1:3, 1:4, 1:8) and the dilutions were incubated on fibrin plates.

Acid stable activity

The other portion of the supernatant was treated with acid. To each ml was added 0.5 ml of the acid solution to give a pH of 1.0. After 15 minutes the solution was neutralized with 0.1 g sodium bicarbonate and dilutions with extraction solution (1:1, 1:2, 1:3, 1:4 and 1:8) were made and incubated on fibrin plates.

After 20 hours incubation at 37°C the lysis areas on all fibrin plates were measured.

From each dilution 3 or 4 incubations were made; the mean values of these lysis areas were calculated for both total activity and acid stable activity. *The mean values* were then plotted on double logarithmic paper with degree of dilution *on the abscissa* and the mean values of the lysis areas on the ordinate.

The nitrogen concentration was determined in the suspension and the lysis area, corresponding to a nitrogen concentration of 0.10 mg nitrogen per

the area of the circumscribed square The mean value of the three or four samples of each dilution was calculated and a curve with the degree of dilution on the abscissa and the lysis areas in mm2 on the ordinate was drawn on double logarithmic paper

Plasminogen free fibrin plate

According to Lassen (1952) the previously described fibrin plate was heated for 35 minutes at 85°C

Another type of plasminogen free fibrin plate was made with plasminogen free fibrinogen and thrombin (Ygge 1970).

Determination of nitrogen in the tissue extract

Nitrogen was determined according to Strid (1961) as modified by Rybo (1966). To 100 µl of a nasal mucosa extract was added 100 µl of the combustion acid.

The mucosa extract and the acid were heated at 400°C for 18 hours on a sand bath After cooling 3 ml 4 M sodium acetate buffer pH 5 5 and 7 ml distilled water were added. Samples of 2 ml were then taken to carry out the ninhydrin reaction. To each 2 ml was added 1 ml ninhydrin reagents. The solution was shaken and the tube was then placed in a boiling water bath for 15 minutes. After cooling 10 ml 50 per cent ethanol was added. The tube was again shaken and the colour determined in a Beckman spektro-photo-meter at 570 nm, with water as a reference

Ammonium sulphate solution containing 1 µg per µl was used as a standard.

To test the error of the nitrogen determination method three different nasal mucosa extracts were made From each extract six samples were analysed. The coefficients of variation in these three extracts were 2.9 3 0 and 3 6 per cent respectively

Standard

Standard tissue plasminogen activator prepared from pig heart (Astrup and Albrechtsen 1957) was kindly supplied by AB KABI Sweden With one or two months intervall a tube with lyophilided pig heart standard was dissolved (6 mg powder per ml extraction solution) The suspension was homogenised in a Potter glass homogenisator at +4°C for 4 minutes at a speed of 500 rpm and then centrifuged at +4°C for 0 minutes at 1700 G. The supernatant was divided into small plastic tubes (one ml in each) and stored at −80°C

In order to investigate whether the fibrinolytic activity in the frozen supernatants changed, when stored at −80°C one batch of tubes with the same frozen supernatant was tested during a period of five months. On 19 different days incubations on fibrin plates were made with the undiluted supernatant (table 3) The mean values of the lysis area was calculated for each day When the mean values from these 19 days were tested with the mean square successive difference test (Brownlee 1965) no significant difference (p > 0 05) was found between the mean values.

Frozen supernatants from five different tubes of lyophilized pig heart standard were tested on 69 different days (table 3). Each day as a rule six incubations were made with one of the defrosted undiluted supernatants. The total mean value of the lysis areas from these 69 days was 441 mm with a standard deviation of 48 mm

Pig heart unit (PHU)

Astrup and Albrechtsen (1957) defined one unit pig heart standard plasminogen activator as the

Table 3 Frozen supernatants from five different tubes of lyophilized pig heart standard were tested on 69 different days.

	Batch number					
	1	2	3	4	5	Total
Test period in days	107	149	128	96	14	183
Number of test days	14	19	14	13	9	69
Number of incubated fibrin plates	70	50	37	33	19	[illegible]
Number of incubations	94	113	76	73	5	411
Range of lysis areas	329 575	356 537	358 564	331 55	376 567	3 9
$\bar{X} \pm$ S.D of lysis area	433 ± 44	439 ± 40	450 44	445 ± 48	446 ± 47	441 48

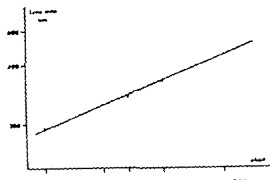


Figure 7 Standard curve On two different occasions, frozen supernatants from three different tubes of lyophilized pig heart standard were diluted with extraction solution On the first occasion each dilution was tested on three different fibrin plates and on the second occasion on six different fibrin plates A total of 27 incubations were made with each dilution (1 1 1.2 1 3 1 4 and 1 8) The mean values from each of these 27 incubations were calculated and standard curve was drawn on double logarithmic paper with degree of dilution on the abscissa and the lysis areas in mm² on the ordinate On the abscissa was also plotted the amount of pig heart units (PHU) per ml

The standard curve was also statistically estimated as regression line, according to the least square method Y 174 274X The correlation coefficient between dilution and lysis area was 0 99

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1 4	251	27	11 %
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lysis area given by one mg lyophilized pig heart standard.

The standard curve

The construction of the standard curve is described in figure 7 It was used as long as the same fibrinogen preparation was used. Each day the standard curve was checked with pig heart standard supernatant. If the mean value of six incubations was within the limit 441±48 mm² the standard curve was accepted.

The pig heart standard supernatant was tested against urokinase (Leo Pharmaceutical Products, Denmark.) With the fibrinogen used in the experiments 6.3 PHU gave the same lysis area on the fibrin plates as Ploug units of urokinase (Three different tubes with ...400 Ploug units of urokinase were diluted with fibrin plate buffer to ? Ploug units of urokinase per ml. The mean value of six incubations from each dilution was calculated.)

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In order to investigate whether the fibrinolytic activity in the frozen supernatants changed when stored at −80°C one batch of tubes with the same frozen supernatant was tested during a period of five months. On 19 different days incubations on fibrin plates were made with the undiluted supernatant (table 3) The mean values of the lysis area was calculated for each day When the mean values from these 19 days were tested with the mean square successive difference test (Brownlee 1965), no significant difference ($p > 0.05$) was found between the mean values.

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	Batch number 1		3	4	5	Total
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Number of incubations	94	113	76	73	55	411
Range of lysis areas	329 575	356 537	358 564	331 55	376 67	3 9 575
$\bar{X} \pm$ S D of lysis area	431 ± 44	439 ± 40	450 ± 44	445 ± 48	446 47	441 48

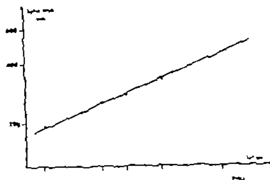


Figure 7. Standard curve. On two different occasions, frozen supernatants from three different tubes of lyophilized pig heart standard were diluted with extraction solution. On the first occasion each dilution was tested on three different fibrin plates and on the second occasion on six different fibrin plates. A total of 27 incubations were made with each dilution (1:1, 1:2, 1:3, 1:4 and 1:8). The mean values from each of these 27 incubations were calculated and a standard curve was drawn on double logarithmic paper with degree of dilution on the abscissa and the lysis areas in mm^2 on the ordinate. On the abscissa is also plotted the amount of pig heart units (PHU) per ml.

The standard curve was also statistically estimated as regression line according to the least square method Y 174 274X. The correlation coefficient between dilution and lysis area was 0.99.

Dilution	Lysis area mm^2 (mean value of 27 determinations)	± S.D.	Variation coefficient (± S.D. in per cent)
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1:8	193	23	12 %

lysis area given by one mg lyophilized pig heart standard.

The standard curve

The construction of the standard curve is described in figure 7. It was used as long as the same fibrinogen preparation was used. Each day the standard curve was checked with pig heart standard supernatant. If the mean value of six incubations was within the limit 441±48 mm^2 the standard curve was accepted.

The pig heart standard supernatant was tested against urokinase (Leo Pharmaceutical Products, Denmark.) With the fibrinogen used in the experiments 6.3 PHU gave the same lysis area on the fibrin plates as 2 Ploug units of urokinase. (Three different tubes with ~400 Ploug units of urokinase were diluted with fibrin plate buffer to Ploug units of urokinase per ml. The mean value of six incubations from each dilution was calculated.)

Method for determination of tissue plasminogen activator

Total activity

The nasal mucosa was weighed and 0.5 ml distilled water per mg of tissue added. Homogenisation was carried out in a Potter glass homogenizator at +4°C for 4 minutes at a speed of 500 rpm. Two samples containing 100 µl each were then taken for nitrogen determination. To the rest of the suspension an equal part of concentrated extraction solution was added. The suspension was homogenised for a further one minute and then centrifuged at +4°C for 20 minutes at 1700 G. The sediment was discharged and the supernatant was divided into two portions. One of the portions was diluted with extraction solution (1:1, 1:2, 1:3, 1:4, 1:8) and the dilutions were incubated on fibrin plates.

Acid stable activity

The other portion of the supernatant was treated with acid. To each 2 ml was added 0.5 ml of the acid solution to give a pH of 1.0. After 15 minutes the solution was neutralized with 0.1 g sodium bicarbonate and dilutions with extraction solution (1:1, 1:2, 1:3, 1:4 and 1:8) were made and incubated on fibrin plates.

After 20 hours incubation at 37°C the lysis areas on all fibrin plates were measured.

From each dilution 3 or 4 incubations were made; the mean values of these lysis areas were calutated for both total activity and acid stable activity. The mean values were then plotted on double logarithmic paper with degree of dilution on the abscissa and the mean values of the lysis areas on the ordinate.

The nitrogen concentration was determined in the suspension and the lysis area, corresponding to a nitrogen concentration of 0.10 mg nitrogen per

ml nasal mucosa extract was read from the dilution curves.

The lysis area corresponding to 0.10 mg N per ml of the total activity was read on the standard curve. The value was multiplied by ten and presented as PHU per mg nitrogen in the nasal mucosa.

The lysis area corresponding to 0.10 mg nitrogen of the acid stable activity was read on the standard curve. The value obtained was multiplied by 1.25 to compensate for the dilution with acid. To get activity per mg nitrogen the value was multiplied by ten. This compensated value was presented as PHUa per mg nitrogen in the nasal mucosa.

Experiments and results

In each experiment three or four incubations of each dilution (1:1, 1:2, 1:3, 1:4, 1:8) were tested. In the experiments presented in table 5–9 and in figure 8 no nitrogen determinations were carried out. In these experiments the mean values of the lysis areas in the undiluted solutions were read on the standard curve and are presented as PHU in the tables.

Extraction

1 Extraction solutions

The results of the extractions with 2 M and 0.15 M *potassium thiocyanate and 2 M and 0.15 M so-*dium chloride at pH 7.0 and 0.15 M potassium *chloride at pH 4.2 are shown in table 4.*

The highest fibrinolytic activity was observed when 2 M potassium thiocyanate was used.

2 Ultra sonic extraction

A piece of nasal mucosa was homogenised with 0.15 M sodium chloride for 15 minutes and then treated with ultra sonic, 250 W for one hour in a thin plastic tube. When tested on fibrin plates the undiluted suspension gave a lysis area of 100 mm^2; after centrifugation the undiluted supernatant gave a lysis area of 30 mm^2. The sediment was dissolved in 2 M potassium thiocyanate, shaken for *one hour and then centrifuged. The supernatant* obtained undiluted gave a lysis area of 570 mm^2.

3 Homogenisation time

After 15 minutes homogenising time (table 5) there was a decrease in activity; after 30 minutes the decrease was more pronounced. For routine purpose a homogenising time of 4 + 1 minutes at a speed of 500 rpm is chosen.

4 Shaking time

As shown in table 6 it is not necessary to shake the tissue suspensions after homogenisation.

Table 5. Homogenising time. A piece of nasal mucosa was homogenised for different lenghts of time at +4°C at a speed of 500 r.p.m. After 2, 5, 15 and 30 minutes, samples were taken from the tissue suspension. The samples were centrifuged at +4°C for 20 minutes (1 700 G) and the supernatant then tested on fibrin plates. The lysis areas, expressed as PHU, given by *different homogenisation time (mi[illegible]tes) are presented.*

	Homogenisation time in minutes			
	2	5	15	30
Experiment 1		46	21	10
2		83	69	48
3	83	75	66	43
4	33	37	29	
5	81	78	83	

Table 4. Effectivity of different extraction solutions. Nasal mucosa was divided and homogenised with the same proportion of the different extraction solutions in the first three experiment. Equal part[illegible] (wet weight) were used in the fourth experiment.

After 5 minutes homogenisation at 500 r.p.m. and +4°C the samples were centrifuged at +4°C for [illegible] minutes at 1 700 G. The potassium chloride solution was then neutralized by 0.4 part of the fibrin plate buffer and tested on fibrin plates together with the undiluted supernatants from the other extraction. Lysis areas in mm^2 (mean [illegible] the incubations) of the different extraction solution are presented.

	2 M KSCN	0.15 M KSCN	M NaCl	0.15 M NaCl	0.15 M KCl pH 4
Experiment 1	430	90	0	130	3[illegible]0
2	595				330
3	670				156
4	484				

Table 6. Shaking time. A piece of nasal mucosa was homogenised for 5 minutes, the tissue suspension was then divided into samples, which were shaken for different length of time at +4°C. The suspensions were centrifuged at +4°C for 20 minutes (1 700 G) and the supernatants tested on fibrin plates. The lysis areas, expressed as PHU at different shaking times, are presented

	Shaking time minutes 0	5	15	30	60	hours 4
Experiment 1		49	51	48	50	51
2	48		42			
3	94		90			

5. Number of extractions

On 51 different occasions a second extraction was made. After homogenising for 5 minutes, the sediment after centrifuging was dissolved in the original volume of extraction solution and shaken at +4°C. After centrifuging the supernatant was tested on fibrin plates. The average activity was 1.2 per cent of the activity in the first extraction.

Thus when small pieces of nasal mucosa are homogenised only one extraction is necessary. Prolonged shaking and further extractions did not give essentially more yield of fibrinolytic activity.

Experiments on acid treatment

6. The correlation between total activity and acid stable activity

On 104 different pieces of nasal mucosa, taken from living subjects, the total activity and the acid stable activity have been determined according to the method described. In none of the determinations was the acid stable activity larger than the total activity. The regression line which describes the relationship between the total activity and the acid stable activity was graphically estimated and was shown to be well approximated by a straight line through the origo. The correlation coefficient between total and acid stable activity was 0.93.

7. Fibrinolytic activity in the tissue extract supernatant and sediment after acid treatment

Supernatants of homogenised nasal mucosa were treated with acid for 15 minutes at different pH. After centrifugation the sediments were dissolved and neutralized and the supernatants dialysed with extraction solution (table 7). After the dialysis the increase of weight of the dialysed supernatant was about four per cent.

As shown in table 7 the dissolved sediments and the dialysed supernatants both contained fibrinolytic activity after acid treatment.

8. Duration of acid treatment

Samples from supernatants of homogenized nasal mucosa were treated with acid solution at pH 1.0 for different lengths of time (table 8). As shown in table 8, the duration of acid treatment, up to 24 hours, seems to be of no importance. For routine purpose 15 minutes is chosen.

Table 7. Fibrinolytic activity in supernatant and sediment after acid treatment. Supernatants of nasal mucosa homogenate were divided into two portions of 4 ml. To each one of the portions acid solution was added to obtain pH 1.2, 1.0, 0.8 or 0.6. After 15 minutes at +4°C the acidified portions were centrifuged at 20 000 G for 20 minutes at +4°C. The sediment were dissolved in 4 ml extraction solution and neutralized with sodium bicarbonate. The supernatants were neutralized by repeated dialysis in large volumes of extraction solution. The dissolved sediments and the dialysed supernatants were tested on fibrin plates. The lysis areas, expressed as PHU are presented

	pH 1.2 sed	pH 1.2 sup	pH 1.0 sed	pH 1.0 sup	pH 0.8 sed	pH 0.8 sup	pH 0.6 sed	pH 0.6 sup
Experiment 1			7	3			8	1
2			7	6			10	6
3			56	22			42	10
4	0	10			8	7		
5	30	24			36	34		
6			14	2				
7			5	2				
8			27	16				
9			38	30				
10			4	7				
11			25	17				
12			90	3				

Table 8 Duration of acid treatment A supernatant of nasal mucosa homogenate was treated with acid solution to pH 1 0 After 5 and 15 minutes, 1 4 6 and 24 hours at +4°C samples were taken from the acidified solution neutralized with sodium bicarbonate and tested on fibrin plates. The lysis areas, expressed as PHU are presented

	Duration of acid treatment					
	minutes		*hours*			
	5	15	1	4	6	24
Experiment 1	17	18	19	15	20	16
2	20	17	18	15	15	16
3	42	42	46	50		
4	48	38		46		
5	8	10	11	12		
6	53			53		47

9 Dilution of the tissue extract supernatant before acid treatment

Supernatants of nasal mucosa homogenate were divided into portions. Two of the portions were not diluted. The other portions were diluted with distilled water or with extraction solution.

After acidification and neutralisation (table 9) the highest fibrinolytic activity was generally found in the portions which were not diluted before the acidification.

Table 9 Dilution of tissue extract supernatant before acid treatment A piece of nasal mucosa was homogenized and centrifuged. The supern tant was divided into por tion of 2 mL Two of the portions (1 and 2) were not diluted The other portions were *diluted 1.3 (portion* number 3) or 1 7 (4) with distilled water and 1.3 (5) or 1 7 (6) w th extraction solution. To all the portions acid solution was added to pH 1 0 After 15 minutes t +4°C the undiluted portion (1) was neutralized with sodium bicarbonate the other portions were centrifuged at +4°C fo 20 minutes at 20 000 G The sediments were dissolved in 2 ml extra tion olution neutralized with sodium bicarbonate and tested on fibrin plates together with portion one The lysis areas, expressed as PHU are presented

	Portion number					
	1	2	3	4	5	6
Experiment 1		11		8		8
2		25		12		21
3		22	17	11	16	
4		52	48	48	48	
5			35	28	32	28
6	18	34		7		4
7	13	6		5		2
8	48	30		22		14

(figure 8)

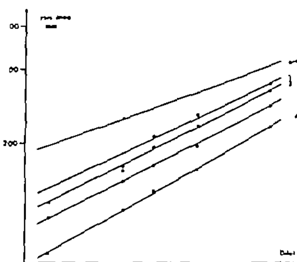


Figure 8 In the figure are shown the dil tion curve experiment 8 in table 9 The number of the curves is same as the number of the p rtions in tabl 9 Contr the untreated centrifuged homogenate The portion which was not diluted before centrifugation was teste two ways. After centrifuging the sediment was dissol and neutralized (7) and the supernatant was dialysed extraction solution (8).

10. Accuracy in reproduction when testing p mortal nasal mucosa

On eight different occasions pieces from the sa frozen nasal mucosa were analyzed according the described method (table 10 and figure 9).

Determinations of the fibrinolytic activity w made in two different ways With the aid o computer *a dilution curve was statistically e* mated as a regression line according to the le square method with the logarithmic values of t dilutions on the abscissa and the logarithmic valu of the mean values of the lysis areas in t *different dilutions on the ordinate On the line t* lysis area corresponding to 0 10 mg nitr gen p ml nasal mucosa extract was numeri ally dete mined by the computer (column II table 10)

A second determination was made graphic all A graph was plotted on double l garithmic pap (as a regression line according to the lea t squa method) with the dilutions on the abscissa and th mean values of the lysis areas in the five diluti n on the ordinate The lysis area rrespending t 0.10 mg nitrogen was read on the graph (lu n III and IV in table 10, figure 9)

The graphically determined lysis area f t total acti ity corresponding to 0 10 mg nitrogen

Table 10. Accuracy in reproduction when testing post mortal nasal mucosa. Eight pieces from the same frozen nasal mucosa were analysed according to the described method. The nitrogen concentration was determined in each tissue extract (I). The lysis area of the total activity corresponding to 0.10 mg nitrogen per ml nasal mucosa homogenate was determined by computer (II) and graphically (III). The lysis area of the acid stable activity corresponding to 0.10 mg nitrogen per ml nasal mucosa homogenate was determined graphically (IV). The values of the lysis areas in (III) and (IV) were read on the standard curve and expressed as PHU and PHUa per mg nitrogen in the nasal mucosa homogenate. The quotient, expressed in per cent, between the acid stable activity and the total activity is called the tissue activator quotient.

Day of experiment	Nitrogen concentration mg per ml nasal mucosa homogenate (I)	Lysis area 0.10 mg N per ml nasal mucosa homogenate (II)	(III)	(IV)	Total activity PHU/mg N	Acid stable activity PHUa/mg N	Tissue activator quotient in per cent
701202	0.104	424	420		54		
701202	0.119	431	450		61		
701117	0.220	382	385		46		
701116	0.070	407	420	340	54	45	83
701103	0.170	407	415	340	53	45	85
701103	0.142	416	415	330	53	43	81
701029	0.092	461	460	370	63	54	86
701026	0.048	411	420	360	54	50	93
	Mean value	417	423	348	55	47	86
	± S.D.	23	23	16	5	5	4
	Variation coefficient (± S.D. in per cent)	5	5	5	10	10	5

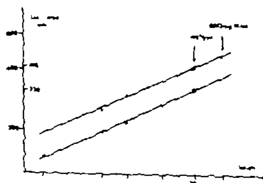


Figure 9. Experiment number 6 (701103) in table 10. The nitrogen concentration in the undiluted tissue extract was 0.284 mg nitrogen per ml. A the tissue extract is diluted once the nitrogen concentration in the undiluted supernatant corresponds to 0.142 mg nitrogen per ml. When the supernatant is diluted to 70.4 per cent it corresponds to 0.10 mg nitrogen per ml of the original extract. The lysis areas of the total activity (curve 1) and the acid stable activity (curve 2) at 0.10 mg nitrogen per ml are read on the ordinate.

per ml nasal mucosa extract was read on the pig heart standard curve and expressed as PHU per mg nitrogen. The acid stable activity was expressed in the same way as PHUa per mg nitrogen.

The variation coefficient of the *total activity* (graphical values), measured as PHU and of acid stable activity *measured as PHUa*, were 10 per cent. As shown in table 10 it is not necessary to use numerical determinations for routine use.

11. Influence of admixture of plasma in nasal mucosa

Different plasmas with a high fibrinolytic activity were added to supernatants of nasal mucosa homogenate. The plasmas used were taken immediately after half an hours heavy exercise on a test bicycle to receive an increased fibrinolytic activity in the plasmas, and frozen at −20°C for about one month.

The amount of plasma correspond approximately to seven times the amount of nasal mucosa wet weight/wet weight. The lysis areas were about the same, irrespective of whether plasma was added or not (table 11). Thus even large amounts of plasma with a high fibrinolytic activity did not change the tissue plasminogen activator activity.

Experiments on the fibrin plates

12. The importance of different fibrinogen preparations

Fibrin plate were made with different fibrinogen solutions and tested with nasal mucosa extract supernatants.

Table 8 Duration of acid treatment A supernatant of nasal mucosa homogenate was treated with acid solution to pH 1 0 After 5 and 15 minutes, 1 4 6 and 24 hours at +4°C samples were taken from the acidified solution *neutralized with sodium bicarbonate* and tested on fibrin plates. The lysis areas, expressed as PHU are presented

	Duration of acid treatment					
	minutes		hours			
	5	15	1	4	6	24
Experiment 1	17	18	19	15	20	16
2	20	17	18	15	15	16
3	42	42	46	50		
4	48	38		46		
5	8	10	11	12		
6	53			53		47

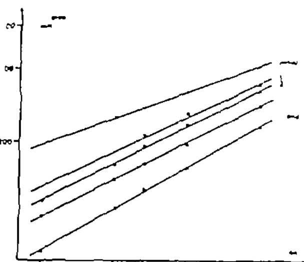


Figure 8 In the figure are shown the dilution curves of experiment 8 in table 9 The number of the curves is the same as the number of the portions in table 9 Control is the untreated centrifuged homogenate The portion (1) which was not diluted before centrifugation was tested in two ways. After centrifuging the sediment was dissolved and neutralized (7) and the supernatant was dialysed in extraction solution (8).

9 Dilution of the tissue extract supernatant before acid treatment

Supernatants of nasal mucosa homogenate were divided into portions. Two of the portions were not diluted. The other portions were diluted with distilled water or with extraction solution.

After acidification and neutralisation (table 9) the highest fibrinolytic activity was generally found in the portions which were not diluted before the acidification.

Table 9 Dilution of tissue extract supernatant before acid treatment A piece of nasal mucosa was homogenized and centrifuged *The supernatant was divided into portion* of 2 ml Two of the portions (1 and 2) were not diluted The other portions were diluted 1 3 (portion number 3) or 1 7 (4) with distilled water and 1 3 (5) or 1 7 (6) with extraction solution. To all the portions acid solution was added to pH 1 0 After 15 minutes at +4°C the undiluted portion (1) was neutralized with sodium bicarbonate the other portion were *centrifuged at +4°C for 20 minutes at 20 000 G The sediment were dissolved* in 2 ml extraction solution neutralized with sodium bicarbonate and tested on fibrin plates together with portion one The lysis areas, expressed as PHU are presented

	Portion number					
	1		3	4	5	6
Experiment 1		11		8		8
2		25		1		21
3		22	17	11	16	
4		5	48	48	48	
5			35	28	32	28
6	18	14		7		4
7	13	6		5		
8	48	30		22		14

(figure 8)

10 Accuracy in reproduction when testing post mortal nasal mucosa

On eight different occasions pieces from the same frozen nasal mucosa were analyzed according to the described method (table 10 and figure 9).

Determinations of the fibrinolytic activity were made in two different ways. With the aid of a computer a dilution curve was statistically estimated as a regression line according to the least square method with the logarithmic values of the dilutions on the abscissa and the logarithmic values of the mean values of the lysis areas in the different dilutions on the ordinate On the line the lysis area corresponding to 0 10 mg nitrogen per ml nasal mucosa extract was numerically determined by the computer (column II table 10)

A second determination was made graphically A graph was plotted on double logarithmic paper (*as a regression line according to the least square* method) with the dilutions on the abscissa and the *mean values of the lysis areas in the line dilutions* on the ordinate *The lysis area corresponding to 0.10 mg nitrogen* was read on the graph (column *III and IV in table 10, figure 9)*

The graphically determined lysis area of the total activity corresponding to 0 10 mg nitrogen

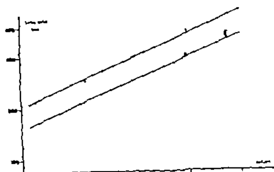


Figure 10. The importance of different buffers in the fibrin plate. Fibrin plates were made, according to the method described, with two different buffers. The plates were tested with nasal mucosa extract supernatant.
Buffer I. Fibrin plate buffer, containing salt solution with Mg^{++} and Ca^{++} in physiological concentrations.
Buffer II. Barbital buffer without the salt solution.
Dilution curves of the two types of fibrin plates are presented.

14. The importance of different buffers

Fibrin plates were made with two different buffers (fibrin plate buffer and barbital buffer) and tested with nasal mucosa extract supernatants.

As shown in figure 10, the highest fibrinolytic activity was observed when a buffer containing Ca^{++} and Mg^{++} in physiological concentrations was used. This buffer was used in the experiments.

15. The importance of different concentrations of agar

Fibrin plates were made without agar and with agar in different concentrations. The different fibrin plates were tested with a nasal mucosa extract supernatant.

As shown in figure 11 the highest fibrinolytic activity was noted in the fibrin plates without agar.

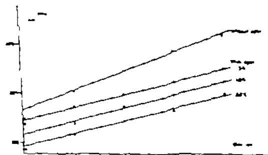


Figure 11. The importance of different concentrations of agar in the fibrin plate. Fibrin plates were made, according to the method described, without agar and with agar in 0.5, 1 and ... per cent. The plates were tested with nasal mucosa extract supernatant. Dilution curves of the four types of fibrin plates are presented.

16. Plasminogen free fibrin plates

On two different occasions fibrin plates were made as described and then heated to 85°C for 35 minutes. Unheated and heated fibrin plates were tested with pig heart standard supernatant and nasal mucosa extract supernatant.

Plasminogen free fibrin plates according to Yggs (1970) were also made and tested in the same way.

No lysis areas were seen on the heated fibrin plates or on the plasminogen free fibrin plates. Thus the supernatants do not contain any detectable amount of plasmin.

Comments

Mainly two methods are used for determination of tissue plasminogen activators, Astrup and Albrechtsen's method (1957) and Todd's method (1959). When using Astrup and Albrechtsen's method 100–1000 mg tissue is required and the extraction takes about six hours. Todd's method can be used to analyse small pieces of tissue but is only semiquantitative. The results of the experiments in this investigation have shown that it is possible to simplify and modify Astrup and Albrechtsen's method and to make it suitable for quantitative analysis of small pieces of nasal mucosa.

Astrup and Albrechtsen correlated the fibrinolytic activity to the wet weight of the tissue. In the present method small pieces of nasal mucosa are used. These pieces dry quickly and the weight loss is of importance. The fibrinolytic activity was therefor correlated to the nitrogen concentration in the nasal mucosa and not to wet weight.

In Astrup and Albrechtsen's method the tissue extract supernatant, after dilution, was acidified with 1 M hydrochloric acid to pH 1.0 and then centrifuged. The sediment was dissolved in 2 M potassium thiocyanate and neutralized with sodium bicarbonate. The sediment was supposed to contain all the activators, and the supernatant to contain the inhibitors. To prove this hypothesis

Table 11 Influence of admixture of plasma in nasal mucosa. Biopsies of nasal mucosa taken from living subjects were homogenized and the nitrogen concentration determined. After centrifuging each supernatant was divided into two portions of 3 ml each. To one portion was added 20 µl plasma with a high fibrinolytic activity. Both protions were then analysed according to the described method. The total activity is expressed as PHU per mg nitrogen and the acid stable activity as PHUa per mg nitrogen of the nasal mucosa homogenate. The fibrinolytic activity in euglobulin precipitate from plasma was determined as described in chapter 3 k.

Experiment number	Plasma number	Lysis area of euglobulin precipitate from plasma	Nasal mucosa number	Total activity PHU	Acid stable activity PHUa	Plasma added: Total activity PHU	Plasma added: Acid stable activity PHUa
1	I	320 mm²	1	63	39	67	44
	II	350	1	69	44	66	41
3	I	320	2	59	21	53	19
4	III	270	3	99	–	99	–

As shown in table 12 the highest fibrinolytic activity was observed when human fibrinogen prepared according to Brakman (1967) was used. *Bovine fibrinogen prepared according to Brakman* (1967) gave about the same lysis areas as human fibrinogen produced by AB KABI Stockholm Sweden. Bovine fibrinogen from AB KABI Stockholm Sweden was not sufficiently sensitive for the analyses.

For routine use fibrin plates were made with bovine fibrinogen prepared according to Brakman. Human fibrinogen was not used for economical reasons.

Six different bovine fibrinogen preparations have been prepared according to Brakman during two years. These six preparations have given about the same lysis areas when tested with the pig heart standard.

Table 12 The importance of different fibrinogen preparations. Fibrin plates were made according to the method described with four different fibrinogen solutions. Fibrinogen concentration in the plate was 1 g per liter (0.1 %). The plates were tested with nasal mucosa extract supernatants.

Fibrinogen I Bovine fibrinogen prepared according to Brakman (1967).
II Human fibrinogen prepared according to Brakman (1967). Three different preparations were tested
III Bovine fibrinogen manufactured by AB KABI Stockholm Sweden
IV Human fibrinogen manufactured by AB KABI Stockholm Sweden.

Mean values of the lysis areas in mm² given by the test solutions are presented

	Fibrinogen I	II	III	IV
Experiment number 1	365	695		390
2	360	747		
3	388	955		
4	475		160	

13 *The importance of different thrombin preparations*

Fibrin plates were made with three different thrombin solutions and tested with nasal mucosa extract supernatants.

As shown in table 13 a slightly higher activity was noted when Topostasin was used. Human crude thrombin before and after gel filtration and ion exchange chromatography gave about the same lysis areas. *Despite the larger lysis areas received* by using Topostasin, purified human thrombin was used instead of Topostasin, which contains plasminogen in different concentrations (Shulte 1965 Berg et al 1966).

Table 13 The importance of different thrombin preparations. Fibrin plates were made according to the method described with three different thrombin solutions, each containing 20 NIH units of thrombin per ml. The plate were tested with nasal mucosa extract supernatant.

Thrombin I Human crude thrombin prepared *according to Berg et al (1966)*
II Human purified thrombin prepared according to Berg et al (1966)
III Topostasin, bovine crude thrombin manufactured by Hoffmann La Roche Co AG Basel, Switzerland

Mean values of the lysis areas in mm² given by the test solutions are presented

	Thrombin I	II	III
Experiment number 1	445	433	500
2	490	480	585

CHAPTER 4

RESULTS

A. The frequency of epistaxis

The frequency of epistaxis was studied in the population sample, the out patients and the hospitalized patients (chapter) by using the answers to questions numbers 5 6 7 and 9 in the questionnaire (chapter 3 A) for statistical analyses.

Results

The incidence of epistaxis in the population. In the population sample was noted that 60 per cent of the subjects (246/410) had suffered from epistaxis at least once in life (appendix 1).

It was also found that 15 per cent of the men (28/190) and 9 per cent of the women (20/220) had single or several bleedings from the nose every year. The difference in frequency between the sexes is not significant (0 10 > p > 0 05)

During the week immediately preceding the week in which the questionnaire was answered 9 subjects (2.2 %) in the population sample had had epistaxis (table 14). All these nine subjects belonged to the group wh had single or several bleedings every year none of them had been treated for epistaxis by doctor

Habitual bleeders. Subjects and patients who said they had several episodes of epistaxis every year were called habitual bleeders. In all age groups there was a higher proportion of habitual bleeders in the out patients than in the population sample (figure 12)

The habitual bleeders constituted 4 per cent of the population sample 2 per cent of the out patients and 8 per cent of the hospitalized patients (appendix 1). Among the out patients the highest proportion of habitual bleeders was observed in the age group less than 20 years old (figure 1?).

Subjects treated for epistaxis. In the population sample 4 subjects (6 %) had at least once been treated for epistaxis by a doctor.

Out of 18 habitual bleeders in the population sample, 14 subjects (78 %) had never been treated for epistaxis by a doctor

Patients treated for epistaxis. Of the out patients 17 per cent and of the hospitalized patients 39 per cent had epistaxis for the first time in life.

By use of the sex and age distribution in the out patients and the inhabitants of Goteborg it was possible to calculate the frequency of subjects

Table 14. A ne subjects in the population sample th epistaxis the previous eek. The answers to question numbers 1 to 5 and 7 to 9 in the questionnaire (chapter 3 A) are presented. Affirmative answers are marked w th ASA acetylsalicylic acid URI pper respiratory infection Question nr 7 frequency of epistaxis, have had several bleedings every year d have had single bleedings every year

Age	Sex	Hypertension history	Hypertension therapy	History of ASA	History of URI	Treatment for epistaxis	Frequency of epistaxis	Epistaxis/ common cold	Epistaxis/ stress
74	w								
55	w								
24	w								
16	m								
13	m								
4	m								
31	m								
25	m						d		
9	w						d	–	
							d		

Astrup and Albrechtssen mixed a pig heart activator solution with an ox lung inhibitor (pulmin) solution. They were able to separate this particular activator from this particular inhibitor by acid precipitation. When the mixture of activator and inhibitor was tested on fibrin plates, they showed that the undiluted mixture gave no lysis but that a lysis area was obtained when the mixture was diluted. The inhibitor thus seemed to have its highest inhibition activity in undiluted solutions.

In none of the determinations of total and acid stable activity in this study has it been possible to demonstrate inhibitors which react like pulmin. The activity in the undiluted solutions has always been higher than in the diluted solutions. If there are inhibitors present in the tissue extract supernatants they seem to have the same inhibition activity in undiluted as in diluted solutions.

When the tissue extract supernatants were *precipitated with acid both the neutralized sediments* and the dialysed supernatants contained activity. The activity therefor must be determined on both the sediments and supernatants. The precipitations have not in any experiment been complete there has always been activity in the dialysed supernatants. Dilution before acid precipitation did not improve the results.

Experiments which were carried out with nasal mucosa have shown that the highest fibrinolytic activity was obtained always when the tissue extract supernatants were tested without acid treatment. Acid treatments always destroyed a varying part of the total activity.

The experiment with ultra sonic extraction showed that the activity in the nasal mucosa was low even if all the cell membranes were destroyed. When the tissue extract was treated with potassium thiocyanate the activator was either released from the tissue extract or the inhibitors were already destroyed at this moment.

Previous investigators (Astrup and Albrechtssen 1957 Rybo 1966 Brakman 1967) prepared a standard curve every day. The variation coefficient between the slopes of the dilution curves from different days in the investigations mentioned were 12 to 16 per cent and between the lysis areas 7 to 15 per cent.

In this investigation the values of the standard curve were based on several incubations from different days. With this mean standard curve a good correlation between dilution and lysis areas was obtained and variations in slope were avoided. The reliability of the standard curve was then checked every day.

The fibrinolytic activity studied by the present method is partly a measure of the amount of vessels in the nasal mucosa and partly a measure of the amount of plasminogen activators in the vessels.

Only small pieces of nasal mucosa (3 to 5 mg) are required for the analyses. At different occasions at least four to six biopsies can be taken from the same individual by means of a Hartman ear polyp forceps. By using these forceps about the same amount of tissue can be taken each time. The biopsies must be taken apart from each other to avoid biopsies with scar tissue.

When eight different parts of the nasal mucosa from one inferior concha were analysed there was a fairly good correlation between the lysis areas corresponding to 0.10 mg nitrogren per ml nasal mucosa extract (variation coefficient five per cent).

This shows that it probably is of minor importance from what part of the concha the biopsy is taken. The amount of activator is obviously equally distributed in these parts of the nasal mucosa. It is thus possible to compare the fibrinolytic activities in biopsies taken at different occasions from the same individual.

the nose than in younger patients (chapter 4 B). It was also more common with distinct arterial bleedings in older patients (chapter 4 B). These bleedings are more difficult to arrest and they might be an explanation to the higher frequency observed.

In the population sample 10 per cent of the subjects had noted an association between epistaxis and stress/fatigue. We have as yet no information to explain in what way stress is correlated to epistaxis.

Conclusions

Epistaxis is a common symptom. In a population sample 60 per cent of the subjects had had epistaxis at least once in life but only one subject of ten, who had had epistaxis, had been treated for it by a doctor.

Subjects who frequently have nose bleedings do not necessarily require professional therapy.

The incidence of epistaxis per year is at least 15 per cent for men and 9 per cent for women.

B. Subjective explanation of the start of nose bleeding, localisation of the bleeding source and the effect of different local treatments

All 1118 registered patients (chapter 2) were asked if they could themselves give any possible explanation to the start of the nose bleeding (chapter 3 A question number 10). The answers which were given are presented.

After the clinical examination of the registered patients the localisation of the bleeding source and the kind of bleeding were classified (chapter 3 B). The results of these classifications are presented together with the results of the local therapy (chapter 3 C).

Results

Subjective explanation of the start of nose bleeding. The nose bleedings started without any obvious reason (when lying in bed, sitting on a chair, washing hands, eating etcetera) in 65 per cent of all patients. The other patients could themselves give possible explanations to the release of the nose bleeding.

Different traumas to the structures of the nasal cavities were primary releasing factors in 28.5 per cent of the patients (table 16).

Physical exhaustion before the release of the nose bleeding was given as explanation by 5 per cent of the patients (for example after lifting heavy things, in connection with sports, after digging).

Psychical exhaustion before and in connection with the start of the nose bleeding was mentioned as explanation by 1.5 per cent of the patients (for example when preparing examinations, work in stress, personal anxieties and sorrows).

In 62 of 111 hospitalized patients the bleeding started without any obvious reason. About one third (20/62) said that the bleeding started between 7 and 9 o'clock in the morning.

Localisation of the bleeding source. The localisation of the bleeding source was somewhat different in different ages. In patients less than 20 years old 91 per cent bled from the nasal septum. Patients more than *40 years old had bleedings* from the nasal septum in 68 per cent (table 17).

The bleeding source was invisible in 5 per cent

Table 16. *Subjective explanation of the start of nose bleeding*

	Per cent of patients in the age group			
	<20	20–39	>40 years	Total
Did the bleeding start				
When you blow your nose	23	24	13	17
When you sneezed	2	4	3	3
After picking the nose	5	5	5	5
After blow on the nose	2	3	2	2
After punctures of sinus	0	6	1	1.5
After psychical exhaustion	5	5	5	5
After physical exhaustion	0	3	2	1.5
Without any obvious reason	63	50	69	65

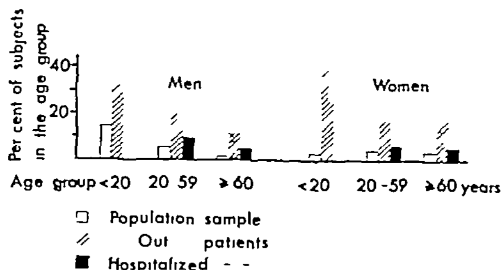


Figure 1 The proportion of habitual bleeders in different age groups.

attending an ENT doctor for epistaxis. In the same way it was also possible to calculate the frequency of subjects being hospitalized due to epistaxis. As shown in table 15 both these frequencies were higher in inhabitants more than 60 years old than in inhabitants less than 60 years old.

Epistaxis associated with stress. According to the answers in the questionnaire a association between stress/fatigue and epistaxis was noted by 40 subjects (10 %) in the population sample 9 of these subjects were habitual bleeders.

Comments

The incidence of epistaxis in a population sample has only been reported by Weiss (1972), who noted that 7 to 14 per cent of the subjects had had epistaxis at least once In this study it was observed that 60 per cent of the subjects in the population sample had had epistaxis at least once in life

Single or several bleedings from the nose every year was observed in 15 per cent of the man and 9 per cent of the women in the population sample. Probably the incidence of epistaxis per year in the population is above the mentioned values, as subjects with a single bleeding during the last year were not registered.

Habitual bleeders were found less frequently in hospitalized patients than in out patients, which shows that there is no strong correlation between habitual bleeding and the severity of nose bleeding.

The occurrence of epistaxis was shown to be poorly correlated to the requirement of treatment by a doctor In the population sample 60 per cent of the subjects had had epistaxis at least once but only 6 per cent of the subjects had been treated for epistaxis by a doctor

The frequency of subjects attending an ENT doctor due to epistaxis was higher per 10.000 inhabitants and year in inhabitants more than 60 years old than in inhabitants less than 60 years old. The bleeding source in older patients was more frequently localized in the posterior parts of

Table 15. The frequency of subjects attending an ENT-doctor due to epistaxis (out patients) and the frequency of subjects being hospitalized due to epistaxis (hosp patients) per 10 000 inhabitants and year in different age and sex groups.

	Men age group					Women age group					
	< 0	0–39	40–59	≥60	in all	< 0	0 39	40 59	≥60	in all	Total
Out patients	16 4	10 1	16 6	31 4	17 4	1 0	5 8	9 3	.5 4	1 5	14 9
Hosp patients	0.1	0 8	3 9	5 1		0 1	0 9	0 9	9	1 1	1 6
Number of inhabitants in the age group x 10 000	5 8	7 8	5 8	1 7		5 6	6.3	6 0	4 9	8	45 0

the nose than in younger patients (chapter 4 B). It was also more common with distinct arterial bleedings in older patients (chapter 4 B). These bleedings are more difficult to arrest and they might be an explanation to the higher frequency observed.

In the population sample 10 per cent of the subjects had noted an association between epistaxis and stress/fatigue. We have as yet no information to explain in what way stress is correlated to epistaxis.

Conclusions

Epistaxis is a common symptom. In a population sample 60 per cent of the subjects had had epistaxis at least once in life but only one subject of ten, who had had epistaxis, had been treated for it by a doctor.

Subjects who frequently have nose bleedings do not necessarily require professional therapy.

The incidence of epistaxis per year is at least 15 per cent for men and 9 per cent for women.

B. Subjective explanation of the start of nose bleeding, localisation of the bleeding source and the effect of different local treatments

All 1118 registered patients (chapter 2) were asked if they could themselves give any possible explanation to the start of the nose bleeding (chapter 3 A question number 10). The answers which were given are presented.

After the clinical examination of the registered patients the localisation of the bleeding source and the kind of bleeding were classified (chapter 3 B). The results of these classifications are presented together with the results of the local therapy (chapter 3 C).

Results

Subjective explanation of the start of nose bleeding. The nose bleedings started without any obvious reason (when lying in bed, sitting on a chair, washing hands, eating etcetera) in 65 per cent of all patients. The other patients could themselves give possible explanations to the release of the nose bleeding.

Different traumas to the structures of the nasal cavities were primary releasing factors in 28.5 per cent of the patients (table 16).

Physical exhaustion before the release of the nose bleeding was given as explanation by 5 per cent of the patients (for example after lifting heavy things, in connection with sports, after digging).

Psychical exhaustion before and in connection with the start of the nose bleeding was mentioned as explanation by 1.5 per cent of the patients (for example when preparing examinations, work in stress, personal anxieties and sorrows).

In 67 of 111 hospitalized patients the bleeding started without any obvious reason. About one third (20/67) said that the bleeding started between 7 and 9 o'clock in the morning.

Localisation of the bleeding source. The localisation of the bleeding source was somewhat different in different ages. In patients less than 20 years old 91 per cent bled from the nasal septum. Patients more than 40 years old had bleedings from the nasal septum in 68 per cent (table 17).

The bleeding source was invisible in 5 per cent

Table 16. Subjective explanation of the start of nose bleeding.

	Per cent of patients in the age group			
	<20	20–39	≥40 years	Total
Did the bleeding start:				
When you blow your nose	23	24	13	17
When you sneezed	2	4	3	3
After picking the nose	5	5	5	5
After blow at the nose	2	3	2	2
After puncture of pimple	6	6	1	1.5
After psychical exhaustion	5	5	5	5
After physical exhaustion	6	3	2	1.5
Without any obvious reason	63	50	69	65

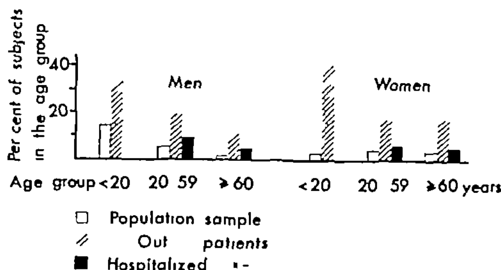


Figure 1 The proportion of habitual bleeders in different age groups.

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Epistaxis associated with stress. According to the answers in the questionnaire a association between stress/fatigue and epistaxis was noted by 40 subjects (10 %) in the population sample 9 of these subjects were habitual bleeders.

Comments

The incidence of epistaxis in a population sample has only been reported by Weiss (1972), who noted that 7 to 14 per cent of the subjects had had epistaxis at least once. In this study it was observed that 60 per cent of the subjects in the population sample had had epistaxis at least once in life

Single or several bleedings from the nose every year was observed in 15 per cent of the man and 9 per cent of the women in the population sample Probably the incidence of epistaxis per year in the population is above the mentioned values, as subjects with a single bleeding during the last year were not registered.

Habitual bleeders were found less frequently in hospitalized patients than in out patients, which shows that there is no strong correlation between habitual bleeding and the severity of nose bleeding.

The occurrence of epistaxis was shown to be poorly correlated to the requirement of treatment by a doctor In the population sample 60 per cent of the subjects had had epistaxis at least once but only 6 per cent of the subjects had been treated for epistaxis by a doctor

The frequency of subjects attending an ENT doctor due to epistaxis was higher per 10.000 inhabitants and year in inhabitants more than 60 years old than in inhabitants less than 60 years old. The bleeding source in older patients was more frequently localized in the posterior parts of

Table 15. The frequency of subjects attending an ENT-doctor due to epistaxis (out patients) and the frequency of subjects being hospitalized due to epistaxis (hosp. patients) per 10 000 inhabitants and year in different age and sex groups.

	Men age group <20	20 39	40 59	≥60	in all	Women age group <20	20 39	40 59	≥60	in all	Total
Out patients	16 4	10 1	16 6	31 4	17 4	12.0	5 8	9 3	25 4	12 5	14 9
Hosp patient	0 1	0.8	3 9	5 1	2.2	0 1	0 9	0 9	2 9	1 1	1 6
Number of inhabitants in the age group x 10 000	5 8	7 8	5 8	3 7	22	5.6	6 3	6 [illegible]	[illegible]	[illegible]	[illegible]

Table 19. Local treatments of epistaxis. During 1 1/2 years 1 118 patients were treated for epistaxis in Goteborg. The primary treatment was successful in 1 003 patients, they had no new bleeding that required new treatment within 24 hours. In 115 patients (10 %) the primary treatment was unsuccessful, they had t be treated second time. The therapy used is listed below

	Primary treatment					
	No therapy	Cauterization with cromic acid	Electrical cauterisation	Spongostan® and Cyklokapron®	Anterior gauze tampons	Posterior Foley and anterior gauz tampons
Number of primary treated patients	73	758	17	156	73	41
Primary treatment successful number of patients		690	13	126	61	40
in per cent		90 %	72 %	78 %	84 %	97 %
	Secondary treatment					
Number of secondary treated patients	0	68	4	30	12	1
Cauterisation with cromic acid		4		2		
Electrical cauterisation		4	4			
Spongostan® and Cyklokapron®		29		5	2	
Anterior gauze tampons		29		14		
Posterior Foley and anterior gauze tampons		2		9	10	1

kapron® (compare chapter 4 H to 4 L) or posterior Foley catheter together with anterior gauze tampons soaked with Cyklokapron® as shown in figure 13

C. Frequency of upper respiratory infections and intake of acetylsalicylic acid

The frequency of histories of upper respiratory infections and intake of acetylsalicylic acid the week before the epistaxis started were studied in the patients and compared with the frequency in the population sample. The subjects in the population sample were asked whether they had noted an association between upper respiratory infections and epistaxis.

Study groups. The following groups were studied. Population sample, out patients and hospitalized patients (chapter 2).

Methods. The answers to questions numbers 3, 4, 7 and 8 in the questionnaire (chapter 3 A) were used for statistical analyses. The distribution of age and sex was different in the population sample and the patient groups. Therefore a division of the study groups into homogenous subgroups with regard to sex and age was performed in order to eliminate the influence of sex and age in the correlations. The occurrences of upper respiratory infections and intake of acetylsalicylic acid in the subgroups of the population sample were correlated to the occurrences in the subgroups of the patients by using contingency tables. The contingency tables from the subgroups were then pooled by a special technique (Odén and Wedel 1974) to get a general conclusion about the correlations in the study groups.

A difference is regarded as significant when $p < 0.01$

Results

In the population sample 30 *per cent of the* subjects had had an upper respiratory infection during the previous week compared with 49 per cent in the out patients and 54 per cent in the hospitalized patients (figure 14, appendix 1). In all age groups the difference was statistically significant between the subjects in the population sample and the patients.

In the population sample 32 per cent of the subjects had taken acetylsalicylic acid during the previous week. The corresponding frequency in *the out patients* was 51 per cent and the hospitalized patients 68 per cent. The difference was *statistically significant in all age* groups between the subjects in the population sample and the patients (figure 14, appendix 1).

It was more common that the patients than the

Table 17 Localisation of the bleeding source

	Per cent of patients in the age group			
	<20	20–39	≥40 years	Total
Kiesselbach area	82	59	47	57
Other parts of septum	9	17	21	17
Lateral parts, floor of the nose	4	10	15	1
Bleeding source not visiable	5	14	17	14

of the patients less than 20 years old and in 17 per cent of the patients more than 40 years old.

In 1.5 per cent (15/1118) of the patients bleeding sources were observed in both nasal cavities.

Kind of bleeding. In 32 per cent of the patients it was impossible to estimate what kind of bleedings the patients suffered from either the bleeding source was not visible or the bleeding too severe. There was no difference between the age groups in this respect (table 18).

In 11 per cent of the patients the nose bleeding had stopped when the patients were examined.

In the ages less than 40 years distinct venous bleedings were more than three times as frequent as distinct arterial bleedings. In patients more than 40 years of age the latter were about as frequent as distinct venous bleedings.

The effect of different local treatments. No therapy was given in 6 per cent of the patients (Table 19). In 68 per cent of the patients the epistaxis was primarily treated with cromic acid cauterisation.

Spongostan® soaked with Cyklokapron® was used instead of anterior gauze tampons in 14 per cent of the patients. The therapy was primarily good in 78 per cent of the treated patients. It was however impossible to arrest severe bleedings which had to be treated with tampons.

Anterior gauze tampons primarily arrested the bleeding in 84 per cent of the treated patients. The unsuccessful cases were treated with posterior Foley catheter and anterior gauze tampons. The nasal mucosa in many cases showed macroscopic signs of inflammatory reaction after the gauze tampon had been taken away finally. This was not observed when Spongostan® soaked with Cyklokapron® was used.

Posterior Foley catheter and anterior gauze tampons primarily arrested the nose bleeding in all cases but one. This therapy was uncomfortable for the patients and required hospitalisation.

Conclusions

The nose bleeding started without any obvious reason when resting in 65 per cent of the patients. In 28.5 per cent of the patients the bleeding was released by different traumas against the structures of the nasal cavities.

The bleeding source was localized on the nasal septum in 91 per cent of the patients less than 20 years old and in 68 per cent of the patients more than 40 years old.

Distinct arterial bleedings were more frequent in patients more than 40 years old than in patients less than 40 years old.

With the therapeutic principles used it was possible to arrest all nasal bleedings. As local therapy of epistaxis is recommended cromic acid cauterisation, Spongostan® soaked with Cyklokapron® anterior gauze tampons soaked with Cyklo-

Table 18 Kind of bleeding.

	Per cent of patients in the age group			
	<20	20–39	≥40 years	Total
Distinct arterial bleeding	11	8	20	16
Distinct venous bleeding	36	28	23	27
Profuse bleeding	11	14	15	14
Impossible to classify	31	34	3	32
No bleeding when examined	11	16	10	11

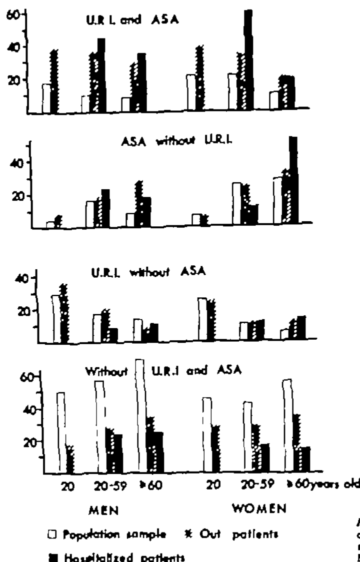


Figure 14. The proportion of histories of upper respiratory infections (U.R.I.) and intake of acetylsalicylic acid (ASA) in different age groups.

subjects in the population sample had taken acetylsalicylic acid when they had an upper respiratory infection (figure 14 appendix 1). In the population sample 15 per cent of the subjects had taken acetylsalicylic acid and had an upper respiratory infection. The corresponding frequency in the out patients was 31 per cent and in the hospitalized patients 43 per cent. In all age groups the difference was statistically significant between the subjects in the population sample and the patients.

In the population sample nine subjects had bled from the nose the previous week. Four of these subjects had taken acetylsalicylic acid when they had an upper respiratory infection (table 14). The combination intake of acetylsalicylic acid and a upper respiratory infection was significantly higher in subjects who had bled the previous week compared with the other subjects.

There was a significant difference in the pooled age groups between the population sample and the patient groups with regard to intake of acetylsali-

Localization and kind of bleeding

Septum | Lateral wall | Treatment





Cotton soaked with lidocain, cromic acid cauterization





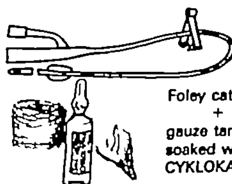
Spongostan® soaked with CYKLOKAPRON®





Gauze tampon soaked with CYKLOKAPRON®





Foley catheter + gauze tampon soaked with CYKLOKAPRON®

distinct bleeding vessel

profuse bleeding area

Figure 13. Local therapy recommended in patients with epistaxis.

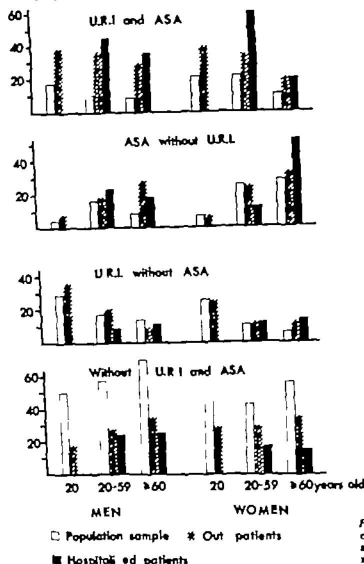


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Localization and kind of bleeding

Treatment

Septum

Lateral wall





Cotton soaked with lidocain, cromic acid cauterization





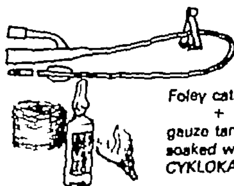
Spongostan® soaked with CYKLOKAPRON®





Gauze tampon soaked with CYKLOKAPRON®





Foley catheter + gauze tampon soaked with CYKLOKAPRON®

distinct bleeding vessel

profuse bleeding area

Figure 13. Local therapy recommended in patients with epistaxis.

All examined pieces of nasal mucosa included the superficial parts of the mucous membrane with mucous and serous glands.

The intensity of the inflammatory reaction was classified in four groups. 0 = no inflammatory reaction + = slight inflammatory reaction with a few leucocytes demonstrable in the epithelium and lamina propria. ++ = moderate inflammatory reaction. Several leucocytes as well as lymphocytes and plasma cells were seen in the epithelium, lamina propria and seromucinous glands. On the surface an exudate of cell detritus and inflammatory cells was observed. +++ = severe inflammatory reaction. A lot of inflammatory cells were seen in the epithelium, lamina propria and seromucinous glands. The epithelium was transformed to stratified squamous epithelium. Cell detritus and inflammatory cells were also observed on the surface of the mucosa.

Results

Histology of the nasal mucosa in the control group

In seven subjects no signs were seen of inflammatory reactions (figure 15). The mucous membrane was covered by columnar ciliated epithelium with goblet cells (figure 16). In older subjects the columnar epithelium was sometimes replaced by a stratified squamous epithelium. The lamina propria contained mucous and serous glands together with a lot of thin walled small vessels. In the lamina propria occasional inflammatory cells such as lymphocytes and plasma cells were frequently observed.

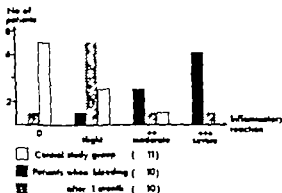


Figure 15. Signs of inflammatory reactions in nasal mucosa biopsies from patients with epistaxis and controls.

Table 20 Point scale of inflammatory reactions in nasal mucosa biopsies, bacterial isolation and leucocyte count in patients with epistaxis

Patient number	Duration of Epistaxis	Histories of URI	ASA	Bacteria when bleeding	Bacteria after one month	Leucocyte count when bleeding	Leucocyte count after one month	Point scale of inflam. reactions when bleeding	Point scale of inflam. reactions after one month
7	1 hour			normal	normal	9 000	8 000		( )
10	2 hours			normal	normal	7 800	7 000	+++	
13	9 day			normal	normal	7 000	5 700	++	
18	7 day			st.a	normal	7 500	7 000	+++	?
37	6 hours			normal	normal	7 200	4 300	+++	( )
45	6 hours			normal	normal	6 000	6 400	++	+
49	4 hours			normal	normal	10 600	5 200	+++	+++
110	2 hours			normal	normal	10 500	5 400	++	
113	2 hours			h.infl.	normal	7 500	7 800	+++	( )
132	9 days	+		st.a	normal	7 600	7 000	+++	++
134	2 hours			normal	normal	6 000	6 000	?	0

too small biopsy

Point scale of inflammatory reaction
+ slight reaction
++ moderate reaction
+++ severe reaction

Normal bacterial isolation means that no potentially pathological bacteria were isolated.

st.a staphylococcus aureus
h.infl. haemophilus influenzae
URI upper respiratory infection
ASA acetylsalicylic acid

the classification of the inflammatory reactions was performed by ass. prof Göran Hansson, Göteborg.

cylic acid among those who had not had an upper respiratory infection. There was also a significant difference in the pooled age groups between the population sample and the patient groups with regard to upper respiratory infections among those who had not taken acetylsalicylic acid

In the population sample 43 subjects (10 %) had noted an association between upper respiratory infections and epistaxis, 12 of these subjects were habitual bleeders.

Comments

During four weeks in the winter when the incidence of upper respiratory infections is known to be high the subjects in the population sample were asked whether they had had an upper respiratory infection and whether they had taken acetylsalicylic acid. If the subjects had been asked throughout the whole year the incidence of upper respiratory infections probably would have been less in the population sample In spite of this the incidence of upper respiratory infections, the week before the question was asked was significantly higher in all age groups of the patients than in all age groups of the population sample.

The results are in accordance with the postulation that histories of upper respiratory infections and intake of acetylsalicylic acid separately might predispose to occasional epistaxis. This is concluded becauce the incidences of upper respiratory infections and intake of acetylsalicylic acid were higher in the patient groups than in the population sample even when patients and subjects were compared within subgroups.

An inflammatory reaction caused by an infection in the nose probably gives a vulnerable mucosa and changes in the vessel walls, which might rupture and start the nose bleeding (compare chapter 1 E and 4 D). Acetylsalicylic acid interfere with the platelet function (Cronberg et al 1970) gives a prolonged bleeding time (Mielke et al 1968 compare chapter 4 G) an impaired primary hemostasis. Even a primary small bleeding might in this way be of clinical importance.

Conclusions

Histories of upper respiratory infections and intake of acetylsalicylic acid were more common in patients with epistaxis than in subjects in the population sample

Subjects in the population sample who had bled the previous week had had an upper respiratory infection during which they consumed acetylsalicylic acid, in a significantly higher frequency than the other subjects in the population sample.

About 10 per cent of the subjects in the population sample had noted an association between upper respiratory infections and nose bleedings.

Together and probably also separately an upper respiratory infection and intake of acetylsalicylic acid might be predisposing to occasional epistaxis.

D Microscopic picture of the nasal mucosa

The aim of this study was to investigate whether any inflammatory reactions could be observed in biopsies taken from the nasal mucosa in patients with epistaxis and to compare the findings in the patients with the findings in the subjects in a control group.

Study groups. Biopsies from the nasal mucosa were taken from 11 randomly selected patients with epistaxis. Five of the patients had bled less than 3 hours, three patients had bled repeatedly more than 7 days. (table 20)

The control groups consisted of 11 healthy subjects (medical assistants or relatives to them) with the same sex and about the same age as the patients. None of the subjects had had an upper respiratory infection the week before the examination.

Methods. All biopsies were taken with an ear polyp forceps (Hartmann) without anestesia. Two biopsies were taken from each patient When the patient bled the first biopsy was taken from the anterior part of the inferior concha on the side opposite to the bleeding. The second biopsy was taken one month later some mm apart from the first

From the subjects in the control group only one biopsy was taken from the anterior part of the inferior concha.

The excised piece of nasal mucosa was immediately fixed in 10 per cent neutral formalin The mucosa was embedded in paraffin and sections 3 micron thick, were stained according to Weigert's modification of van Giesen's haematoxylin method. Some sections were stained with haematoxylin and eosin.

All examined pieces of nasal mucosa included the superficial parts of the mucous membrane with mucous and serous glands.

The intensity of the inflammatory reaction was classified in four groups. 0 = no inflammatory reaction. + = slight inflammatory reaction with a few leucocytes demonstrable in the epithelium and lamina propria. ++ = moderate inflammatory reaction. Several leucocytes as well as lymphocytes and plasma cells were seen in the epithelium, lamina propria and seromucinous glands. On the surface an exudate of cell detritus and inflammatory cells was observed. +++ = severe inflammatory reaction. A lot of inflammatory cells were seen in the epithelium, lamina propria and seromucinous glands. The epithelium was transformed to stratified squamous epithelium. Cell detritus and inflammatory cells were also observed on the surface of the mucosa.

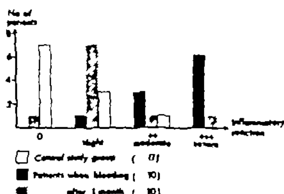


Figure 15. Signs of inflammatory reactions in nasal mucosa biopsies from patients with epistaxis and controls.

Results

Histology of the nasal mucosa in the control group

In seven subjects no signs were seen of inflammatory reactions (figure 15). The mucous membrane was covered by columnar ciliated epithelium with goblet cells (figure 16). In older subjects the columnar epithelium was sometimes replaced by a stratified squamous epithelium. The lamina propria contained mucous and serous glands together with a lot of thin walled small vessels. In the lamina propria occasional inflammatory cells such as lymphocytes and plasma cells were frequently observed.

Table 20. Point scale of inflammatory reactions in nasal mucosa biopsies, bacterial isolation and leucocyte count in patients with epistaxis

Patient number	Duration of Epistaxis	Histories of URI ASA	Bacteria when bleeding	Bacteria after one month	Leucocyte count when bleeding	Leucocyte count after one month	Point scale of inflam. reactions when bleeding	Point scale of inflam. reactions after one month
7	1 hour		normal	normal	9 000	8 000		( )
10	2 hours		normal	normal	7 800	7 000	+++	
13	9 days		normal	normal	7 000	5 700	++	
18	7 days		st.a.	normal	7 500	7 000	+++	?
37	6 hours		normal	normal	7 200	4 300	+++	( )
45	6 hours		normal	normal	6 000	6 400	++	
49	4 hours		normal	normal	10 600	5 200	+++	+++
110	2 hours		normal	normal	10 500	5 400	++	
118	2 hours		h.infl.	normal	7 500	7 800	+++	( )
132	9 days		st.a	normal	7 600	7 000	+++	++
134	2 hours		normal	normal	6 000	6 000	?	0

*too small biopsy

Point scale of inflammatory reaction
+ slight reaction
++ moderate reaction
+++ severe reaction

Normal bacterial isolation means that no potentially pathological bacteria are isolated.

st.a staphylococcus aureus
h.infl. hemophilus influenzae
URI upper respiratory infection
ASA acetylsalicylic acid

The classification of the inflammatory reactions was performed by ass. prof Göran Hansson, Göteborg.

In three subjects a slight and in one subject a moderate inflammatory reaction was observed

*Histology of the nasal mucosa in patients with epistaxis** In all biopsies from the bleeding patients signs of inflammatory reactions were seen in the nasal mucosa (figure 15 table 20) In six of the biopsies the reactions were severe (figure 17) and in three they were moderate

The biopsies that were taken one month after the bleeding also showed inflammatory cells in the mucosa but the inflammatory reaction was less pronounced that one month before

Table 20 shows the duration of epistaxis before the biopsies were taken, the result of bacteriological isolation and the leucocyte count. As seen six patients had had an upper respiratory infection the week before the bleeding started three patients had growth of potentially pathological bacterial strains in the nose (staphylococcus aureus and hemophilus influenzae) and two patients had leucocyte count over the reference value 9 000/ mikroliter

Comments

In all patients with epistaxis inflammatory reactions were seen in the nasal mucosa biopsies, taken from the side opposite to the bleeding side Five of the patients had only bled during one to two hours and it is doubtful that a nose bleeding in the other nasal cavity during this short time should give an inflammatory reaction of the observed magnitude in the examined nasal cavity

Most patients had a leucocyte count within the reference value The increased number of leucocytes observed in the nasal mucosa biopsies was thus not refound in the blood.

In only three patients potentially pathological bacterial strains were isolated in the nose Thus the inflammatory reaction in the nasal biopsies can not in most cases be explained by localized bacterial infections.

Conclusion

It is obvious that patients with epistaxis have inflammatory reactions in the nasal mucosa when they bleed and that these reactions probably are not caused by but a cause of the nose bleeding, indicating that a damaged mucosa is more vulnerable

* the classification of the inflammatory reactions was performed by as prof Goran Ha son Göteborg

In some patients the inflammatory reactions observed might be due to upper respiratory infections.

E. Frequency of histories of hypertension

In order to investigate whether hypertension was associated with nose bleedings or not the frequency of histories of hypertension in patients with epistaxis was compared with the frequency in the population sample

In a study of 5 223 patients with hypertension was shown that only 50 per cent of the patients knew that they had hypertension. (Wilhelmsen 1973). It is thus very possible that the frequency of hypertension in this study is greater than the frequency of histories indicates.

As it is an established truth that hypertension gives nose bleedings one might postulate that all patients with epistaxis who knew that they had hypertension would report it In this way the frequency of reported histories of hypertension might be higher in the patient groups than in the population sample

Study groups. The following groups were studied population sample out patients and hospitalized patients (chapter ?)

Methods The answers to questions numbers 1 2 3 4 and 7 in the questionnaire (chapter 3 A) were used for statistical analyses

The subjects in the population sample and the patients with a *history of hypertension* were subdivided into age groups in order to avoid the influence of sex and age in the analysis. The frequency of histories of hypertension in the subgroups of the population sample was correlated to the frequency in the subgroups of the patients by using contingency tables The contingency tables were then pooled as described in chapter 4 C

Results

Occasional nose bleedings. When the different age groups were pooled there was no statistical difference in the frequency of histories of hypertension between the out patients and the subjects in the population sample ($p = 0.31$)

The analysis indicated instead that it was somewhat more common with histories of hypertension in the population sample than in the



Figure 16. Microscopic picture of nasal mucosa without signs of inflammatory reactions. 192.

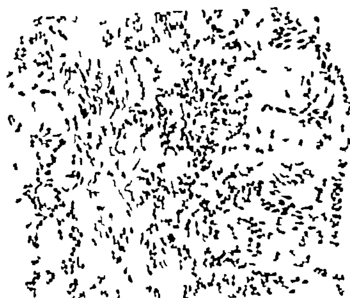


Figure 17. Microscopic picture of nasal mucosa with signs of severe inflammatory reaction. 192.

out patients (figure 18 appendix 1). Only in the age group of men, aged 40 to 59 years, a higher frequency of histories of hypertension was noted in the out patients than in the population sample ($p < 0.01$).

The different age groups of the hospitalized patients were compared with the same groups of the population sample with regard to the frequency of histories of hypertension. Only in the group of men, aged 40 to 59 years, a significantly higher frequency ($p = 0.04$) of histories of hypertension was noted in the hospitalized patients compared with the population sample.

The six hospitalized men with histories of hypertension, in the age group 40 to 59 years, were analysed separately. It was found that three patients were alcoholics and had elevated transaminase values (chapter 4 G), one patient was an

In three subjects a slight and in one subject a moderate inflammatory reaction was observed

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Comments

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In some patients the inflammatory reactions observed might be due to upper respiratory infections.

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As it is "an established truth" that hypertension gives nose bleedings one might postulate that all patients with epistaxis who knew that they had hypertension would report it In this way the frequency of reported histories of hypertension might be higher in the patient groups than in the population sample

Study groups. The following groups were studied population sample out patients and hospitalized patients (chapter 2)

Methods The answers to questions numbers 1 2 3 4 and 7 in the questionnaire (chapter 3 A) were used for statistical analyses.

The subjects in the population sample and the patients with a history of hypertension were subdivided into age groups in order to avoid the influence of sex and age in the analysis. The frequency of histories of hypertension in the subgroups of the population sample was correlated to the frequency in the subgroups of the patients by using contingency tables The contingency tables were then pooled as described in chapter 4 C.

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The analysis indicated instead that it was somewhat more common with histories of hypertension in the population sample than in the

alcoholic with transaminase values within the reference values, one patient had elevated transaminase values but was not an alcoholic and one patient had thrombocytopenia and impaired blood coagulation.

Patients and subjects in the population sample with histories of hypertension had taken acetylsalicylic acid without having an upper respiratory infection in a higher frequency ($p < 0.05$) than those with no histories of hypertension (figure 19).

The frequency of patients with hypertension who were treated with drugs was equal in the hospitalized patients and in the population sample (figure 19).

In patients more than 40 years old it was noted that 21 per cent (37/175) of the patients with a history of hypertension had distinct arterial bleeding. In the same age group 19 per cent (99/514) of the patients without a history of hypertension had distinct arterial bleeding. The difference is not significant.

Habitual bleedings. In the population sample no habitual bleeder was found among 62 subjects with a history of hypertension (figure 19).

Among 148 out patients with a history of hypertension 21 habitual bleeders were observed. No systematical research for other possible predisposing diseases or conditions were performed during the registration of the out patients. Spontaneous notations of such diseases or conditions as dicumarolthterapy, inherited thrombocytopenia, Morbus Osler, papilloma nasi, anterior septal perforations were however made by the examining doctor in 8 of these habitual bleeders. The frequency of habitual bleeders was higher in out patients without a history of hypertension than in those with the latter.

Among 32 hospitalized patients with a history of hypertension were found 2 habitual bleeders, one of these patients had a family history of epistaxis and the other was a chronic alcoholic with severe abnormal transaminase values.

Comments

Hypertension is often mentioned as an etiological factor of epistaxis (compare chapter 1 B). In investigations of Shaheen (1970) and Weiss (1972) no association between epistaxis and hypertension was observed.

When the possible association between histories of hypertension and epistaxis was investigated in this clinical study difficulties in evaluating predisposing factors became obvious. As mentioned in chapter 4 C histories of upper respiratory infections and intake of acetylsalicylic acid might be predisposing to occasional nose bleeding.

Irrespective of a difference in frequency of histories of upper respiratory infection and intake of acetylsalicylic acid, a lower frequency of histories of hypertension was found in the out patients than in the population sample.

A significantly higher frequency of histories of hypertension was only observed in male patients between 40 and 59 years compared with the population sample.

Other diseases than upper respiratory infections might interfere with the statistical analyses in this age group. It was noted that four out of six of the hospitalized men in this group were alcoholics. The frequency of alcoholics in the population sample and the out patients is unknown and it is thus impossible to estimate to what extent the difference in frequency of histories of hypertension between the population sample and the patients was a difference in frequency of alcoholics.

Distinct arterial bleedings were not more common in patients with a history of hypertension than in the other patients. This indicates that a history of hypertension does not separately increase the risk of getting a visible arterial bleeding.

When patients with other possible explanations of habitual bleedings were excluded it was found that no subject in the population sample, no hospitalized patient and 13 out patients with histories of hypertension were habitual bleeders. It was also noted that habitual bleedings were less frequent in patients and subjects with a history of hypertension than in patients and subjects without. A history of hypertension did not seem to predispose to habitual nose bleedings.

Conclusion

The results of the statistical analyses indicate that a history of hypertension probably is not related to nose bleedings.

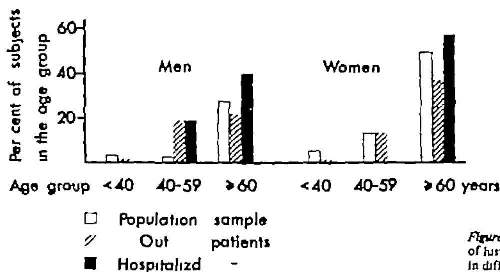


Figure 18. The proportion of histories of hypertension in different age groups

Per cent of subjects in the group

100, 80, 60, 40, 20

History of hypertension	Population sample +	Population sample −	Out patients +	Out patients −	Hospitalized pat +	Hospitalized pat −
Number of subjects						
In the group n	62	348	148	859	32	79
— — with habitual bleedings n	0	18	21	200	2	7
— — treated for hypertention n	43				15	

Upper respiratory infection

Upper respiratory infection and intake of acetylsalicylic acid

Intake of acetylsalicylic acid

Figure 19. Patient and subjects with ( ) and without ( ) a history of hypertension correlated to the frequency of histories of upper respiratory infection and intak of acetylsalicylic acid

alcoholic with transaminase values within the reference values, one patient had elevated transaminase values but was not an alcoholic and one patient had thrombocytopenia and impaired blood coagulation.

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A significantly higher frequency of histories of hypertension was only observed in male patients between 40 and 59 years compared with the population sample.

Other diseases than upper respiratory infections might interfere with the statistical analyses in this age group. It was noted that four out of six of the hospitalized men in this group were alcoholics. The frequency of alcoholics in the population sample and the out patients is unknown and it is thus impossible to estimate to what extent the difference in frequency of histories of hypertension between the population sample and the patients was a difference in frequency of alcoholics.

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Comments

Hypertension is often mentioned as an etiological factor of epistaxis (compare chapter 1 B). In investigations of Shaheen (1970) and Weiss (1972)

Conclusion

The results of the statistical analyses indicate that a history of hypertension probably is not related to nose bleedings.

F Registrated blood pressures

The blood pressure values of patients who had had epistaxis were compared with the values of a control group in order to study whether there was any difference between the patients and the controls.

Study groups. The following groups were studied 1 Extensively examined patients (chapter 2) 2. A population sample from Bergen Before this investigation started it was deceided to use a population sample containing 23 794 inhabitants of Bergen Norway (Boe 1957) as a reference group

Methods. The blood pressure was measure as described in chapter 3 D

As the Bergen population sample consisted of many subjects it was possible to calculate the mean and standard deviation of the blood pressure in age classes with five years interval In the present investigation such a grouping was impossible to use as each group then would contain only a few patients In order to test statistically whether there was any difference in blood pressure between the Bergen population sample and the present patients, it was decided to use sign tests The mean values of blood pressure in the different age groups in the Bergen population sample were connected and the blood pressures of the patients were then plotted and compared with these mean value lines.

Results

No significant differences in blood pressure were noted between the patients and the Bergen population sample tested with sign tests (figure 20 and 21)

The mean values and the standard deviations in different age groups of the patients are presented in figure 22 and 23 together with the mean values and standard deviations in some age groups of the Bergen population sample

Comments

According to Boe (1957) it is inwise to compare the results from blood pressure registrations in different study groups as the blood pressure might be taken during different conditions When this investigation started precautions were taken to measure the blood pressure in the patients in the same way as in the Bergen population sample There might however be slight differences between the measurements all the same

In the present study the blood pressure of the patients were measured some weeks after the actual bleeding. It is known that extensive bleedings cause a drop in blood pressure due to decreased blood volume It is, however unlikely that the blood volume should be decreased some weeks after the actual bleeding, and in this way cause a lower blood pressure than normally

By using the described test model the definition problem of hypertension is avoided As shown in figure 20 and 21 there was no significant difference in systolic and diastolic blood pressure between the patients and the Bergen population sample

Conclusion

The distribution of different blood pressures was the same in the examined patients who had had epistaxis as in a population sample

G Clinical observations and laboratory data in 155 extensively examined patients

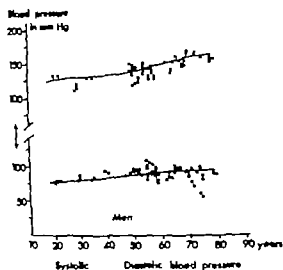
The patients who were studies in this chapter are presented in chapter 2 The methods which were used are described in chapter 3 A F G H The statistical analyses were performed with contingency tables.

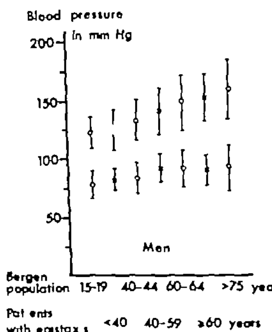
Clinical observation

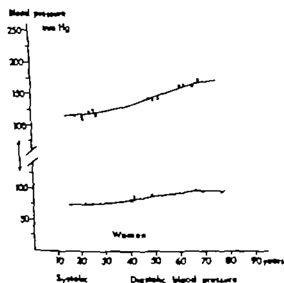
Family history of epistaxis. In the study group 41 patients (26 %) had near relatives (parents children brothers or sisters) who used to bleed from the nose frequently Ten of the patients had more than two relatives with a history of frequent nose bleedings. There was a significantly higher frequency ($p < 0.02$) of habitual bleeders among the patients with family history of epistaxis than among the other patients.

No difference was observed in the frequency of abnormal values of routine tests of hemostatis between patients with family history of epistaxis and patients without (table 21)

History of bleeding tendency All patients were asked if they used to get hematomas on the arms or on the body without traumas and if they used to bleed for a long time after a tooth extraction or after slight skin cuts. An affirmative answer to one







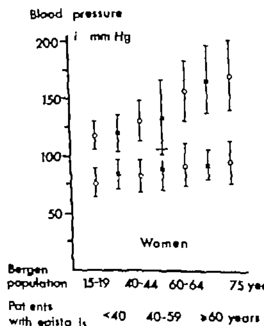


Figure 20 and 21 The blood pressures of the patients in the present study are plotted according to age. Solid lines indicate mean values of blood pressure in the Bergen population.

Figure 22 and 23 Mean values and standard deviations of systolic and diastolic blood pressure in different age groups of patients with epistaxis ( ) and in some age groups of the Bergen population (•—).

or more of these questions was given by 28 patients (18 %)

The frequency of abnormality in one or more of the routine tests of hemostasis was 57 per cent in patients with a history of bleeding tendency and 38 per cent in patients without The difference was not significant. Five patients with a history of bleeding tendency were habitual bleeders (table 21)

Habitual bleeding In the studied group 17 patients (11 %) used to bleed several times every year The frequency of abnormality in one or more of the routine tests of hemostasis was 41 per cent in the habitual bleeders and thus the same as the group in all (table 21)

Other diagnosed diseases The number of patients with diagnosed diseases known by the patient or discovered at the examination are presented in table 22

Alcoholism All patients were asked if they had been hospitalized any time on account of abuse of alcohol. An affirmative answer was given by 22 patients. A strong smell of alcohol was found in 10 of these patients when they were examined Further 4 patients had a strong smell of alcohol but denied hospitalisation on account of abuse of alcohol They admitted however that they were "moderate to severe" drinkers. In all 26 patients (17 %) were assumed to be alcoholics.

Only two of the alcoholics were women, they were more than 60 years old The largest group of alcoholics were 16 men observed in the age group between 40 and 59 years old containing 39 men.

Abnormality in one or more of the blood clotting tests were found in 3 alcoholics. Two of the alcoholics were habitual bleeders (table 21).

Laboratory data

Leucocyte count (LC) C-reactive protein (CRP) erythrocyte sedimentation rate (ESR) antistreptolysine titer (AST) and antistaphylolysine titer (ASTA). When the study was planned it was decided to try to separate viral upper respiratory infections from potent acute bacterial upper respiratory infections. The reason for this separation was the assumption that more pronounced injuries to the nasal mucosa would be caused by potent acute bacterial infections than by viral infections. The macroscopic appearance of the nasal mucosa was regarded as unsuitable for this separation

Patients in whom a potent acute bacterial infection could be diagnosed for certain were patients with an acute sinusitis diagnosed by puncture By use of the unspecific tests LC CRP and ESR together with the specific tests AST and ASTA attempts were made to get a basis for the differentiation between viral and potent acute bacterial upper respiratory infections.

Laboratory signs of a potent acute bacterial infection were found in 32 patients (21 %) as shown in table 23 Among 75 patients with a history of an upper respiratory infection 22 patients (29 %) had laboratory signs of a potent

Table 21 Number of patients with habitual bleedings and abnormal values of routine tests of hemostasis. The routine tests of hemostasis (R.t.o h.) are presented in chapter 3 H. Abbreviations used in the table Cap fr capillary fragility Bl.t. ASA = bleeding time in patients who have taken acetylsalicylic acid Bl t = bleeding time in patients who have not taken acetylsalicylic acid Pl.c. = platelet count B.clot. = blood clotting tests Hab.bl. habitual bleedings.

	Number of patients							
		with abnormal values of					at least one of the R.t.o.h.	with Hab bl
	Total	Cap.fr	Bl t. ASA	Bl.t.	Pl.c.	B clot		
All patients	155	19	16	4	13	35	64 (41 %)	17
Patients with								
Family history of epistaxis	41	5	6	1	4	11	19 (46 %)	9
History of bleeding tendency	28	5	5	2	5	11	16 (57 %)	5
Hematomas on arm	24	4	4	2	5	10	14	3
on body	2	0	0	1	2	2	2	0
After tooth extraction	11	2	2	0	0	4	6	3
After slight skin cuts	2	0	1	1	2	2	2	1
Habitual bleedings	17	1	4	0	3	4	7 (41 %)	17
Alcoholism	26	4	2	1	3	3	11 (42 %)	2
Abnormal transaminase values	40	4	4	1	3	6	13 (33 %)	4

Table 22. Number of patients with diagnosed disease

Diagnosis	Number of patients with diagnosed disease known by the patient	discovered at the examination	total	Number of habitual bleeders with the disease
Diabetes mellitus	8	0	8	0
Arthritis	19	0	19	2
Cardiac disease treated with dicoumarol	3	0	3	0
Alcoholism	22	4	26	2
Pulmonary diseases				
Tuberculosis	0	2	2	0
Pulmonal carcinoma	1	1	2	1
Bronchopneumonia	1	0	1	1
Haematological diseases*				
Macroglobulinemia Waldenström	2	1	3	2
Morbus Osler	1	0	1	1
Anaemia not caused by the actual bleeding	4	–	4	0
Nasal diseases				
Acute sinusitis	10		10	0
Septal perforation	0	4	4	1
Nasal polyps	0	5	5	1
Nasal carcinoma	0	1	1	1
Nasal hemangioma	0	1	1	0

* the number of patients with defects in the hemostasis is presented page 48

Table 23. Number of patients with laboratory signs of potent acute bacterial infection. A patients was regarded to have laboratory signs of potent acute bacterial infection if one or more of the following conditions were fulfilled.
1. Leucocyte count (LC) more than 13 000/microliter in the first blood sampling and less than 9 000/microliter in the second sampling.
2. C-reactive protein (CPR) more than 10 μg/ml in the first blood sampling and decrease of more than 50 per cent in the second blood sampling.
3. Erythrocyte sedimentation rate (ESR) more than 30 mm/hr in men or 38 mm/hr in women in the first blood sampling and decrease of more than 50 per cent in the second blood sampling.
4. A difference of two titer steps or more in antistreptolysine titer (AST) between the two examinations.
5. A difference of two titer steps or more in antistaphylolysine titer (ASTA) between the two examinations.

	Total	Number of patients with laboratory signs of LC	CPR	ESR	AST	ASTA	at least one sign
Patients with							
No history of upper respiratory infection	80	1	7	0	2	0	10 (13 %)
History of upper respiratory infection	75	4	16	6	2	0	22 (29 %)
Diagnosed acute sinusitis	10	1	3	0	0	0	4 (40 %)

acute bacterial infection. It must, however, be stressed that only four of the ten patients with a diagnosed acute sinusitis had laboratory signs of a potent acute bacterial infection.

Among the remaining 80 patients, who had not had any upper respiratory infection the week before they came to the hospital were found 10 patients (13 %) with laboratory signs of a potent acute bacterial infection. No search was carried out to localize the infections in these ten patients.

None of the examined patients with leucocyte count values above the reference value had leucemia.

Creatinine in serum. None of the patients were uremic. In 1 patients (8 %) the kidney function appeared to be impaired, the creatinine concentration being above the reference value but less than 1.8 mg/100 ml.

Transaminases in serum. In 40 patients (26 %) the values of aspartate aminotransferase (GOT)

or more of these questions was given by 28 patients (18 %)

The frequency of abnormality in one or more of the routine tests of hemostasis was 57 per cent in patients with a history of bleeding tendency and 38 per cent in patients without The difference was not significant. Five patients with a history of bleeding tendency were habitual bleeders (table 21)

Habitual bleeding In the studied group 17 patients (11 %) used to bleed several times every year The frequency of abnormality in one or more of the routine tests of hemostasis was 41 per cent in the habitual bleeders and thus the same as the group in all (table 21)

Other diagnosed diseases. The number of patients with diagnosed diseases, known by the patient or discovered at the examination are presented in table 22.

Alcoholism. All patients were asked if they had been hospitalized any time on account of abuse of alcohol. An affirmative answer was given by 22 patients. A strong smell of alcohol was found in 10 of these patients when they were examined Further 4 patients had a strong smell of alcohol but denied hospitalisation on account of abuse of alcohol They admitted however that they were "moderate to severe drinkers. In all 26 patients (17 %) were assumed to be alcoholics

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Alcoholism	26	4	2	1	3	3	11 (42 %)	2
Abnormal transminase values	40	4	4	1	3	6	13 (33 %)	4

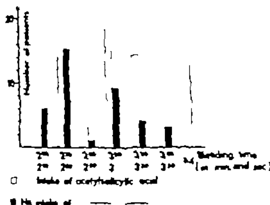


Figure 24 Bleeding time (Duke) in patients without thrombocytopenia with regard to intake of acetylsalicylic acid the previous week.

sured in all patients on at least three occasions. The values measured at the first examination and the values which were measured 2 to 4 days after the bleeding was finally arrested are presented in figure 25 to 28.

When the hemoglobin value which was measured 2 to 4 days after the bleeding was finally stopped, was below the reference value the patient was assumed to have anemia. It was found that 43 per cent of the out patients and 73 per cent of the hospitalized patients had a hemoglobin value below the reference value indicating that they were anemic.

The decrease in hemoglobin concentration between the first blood sampling and the blood sampling 2 to 4 days after the bleeding was finally arrested was 1.3±1.3 g/100 ml in the hospitalized patients and 0.7±0.7 g/100 ml in the out patients.

The number of reticulocytes were counted in all patients on at least three occasions. The values measured at the first examination and the values which were measured 4 to 8 days after the bleeding was finally stopped are presented in figure 29 to 32.

Mean values and standard deviation of the reticulocyte count values which were measured 4 to 8 days after the bleeding was finally arrested were in the hospitalized patients 28±16 and in the out patients 22±14 reticulocytes per 1000 counted erythrocytes. It was found that only 2 patients (1.5 %) had reticulocyte count values within the reference value.

There was no statistically significant difference between patients with hemoglobin values less than 10 g/100 ml and the other patients with respect to family history of epistaxis, history of bleeding tendency, habitual bleeding, histories of upper respiratory infections, intake of acetylsalicylic acid or hypertension. Neither was there found any higher frequency of patients with hemoglobin values less than 10 g/100 ml in patients with elevated values of creatinine in serum, abnormal transaminase values or abnormal values of routine tests of hemostasis.

Blood transfusions were given to 16 of the hospitalized patients.

Blood group. In 75 hospitalized patients blood group determinations were performed. The frequency of different blood groups (ABO) was the same in the patients as in the population of Sweden (table 27).

Table 27 Number of patients with different blood groups

	Blood group 0	A	B	AB
Patients with epistaxis				
Number	28	39	6	2
Per cent	37	52	8	3
Population in Sweden (%)	37	47	11	5

Comments

Patients who were habitual bleeders had a family

Table 26 Number of patients with abnormal bleeding time thrombocytopenia and intake of acetylsalicylic acid (ASA)

	Normal bleeding time Platelet count <150 000	Normal bleeding time Platelet count >150 000	Abnormal bleeding time Platelet count <150 000	Abnormal bleeding time Platelet count >150 000
Number of patients with				
intake of ASA	3	71	3	13
no intake of ASA	1	42	4	0

Table 24 Number of patients with abnormal transaminase values. Abbreviations used in the table GOT = aspartate aminotransferas GPT = alanine aminotransferas.

	Total	Number of patients with abnormal values of GOT	GPT
All patients	155	40 (26 %)	19 (13 %)
assumed alcoholics	26	18 (69 %)	9 (34 %)
not assumed to be alcoholics	129	22 (17 %)	10 (8 %)
Men in age group 40 59 years	39	19 (48 %)	9 (23 %)
assumed alcoholics	16	12 (75 %)	5 (32 %)
not assumed to be alcoholics	23	7 (30 %)	4 (17 %)
Population study (Tiblin et al 1974)	803	72 (9 %)	41 (5 %)

were above the reference value (= abnormal value) and in 19 of these patients the values of alanine aminotransferas (GPT) were above the reference value (= abnormal value) (Table 24)

The frequency of abnormal transaminase values was significantly higher in patients assumed to be alcoholics than in the other patients ($p < 0.01$)

Among 39 male patients between 40 and 59 years of age 19 were observed with abnormal values of transaminases (table 24) The frequency of abnormal values of transaminases in this age group was compared with a population study (Tiblin et al 1974) consisting of 803 randomly selected fiftyfour years old men The frequency of abnormal values of transaminases was significantly higher in patients with epistaxis than in this population study ($p < 0.01$)

Among the patients with abnormal values of transaminases were found 13 patients with abnormality in one or more of the routine tests of hemostasis two of these patients were habitual bleeders A further 2 patients with abnormal transaminase values were habitual bleeders (table 21)

Routine tests of hemostasis. As shown in tables 21 and 25 abnormal values in at least one of these routine tests of hemostatis were observed in 64 patients (41 %) Abnormal capillary fragility was registered in 15 per cent of the patients. The number of platelets was less than 150 000 platelets/mikroliter in 9 per cent and the bleeding time was abnormal in 15 per cent of the patients. Abnormality in at least one of the blood clotting tests were noted in 23 per cent of the patients.

The values of the bleeding time were abnormal in 20 patients when they were examined the first time In 7 of these patients the platelet count was less than 150 000 platelets/mikroliter All the other 13 patients with abnormal values of the bleeding time had taken acetylsalicylic acid some time during the week before they came to the hospital (table 26)

In 117 patients who had a platelet count of more than 150 000 platelets/mikroliter the bleeding time was measured according to Duke The bleeding time was significantly longer ($p < 0.01$) among the patients who had taken acetylsalicylic acid than among those who had not (figure 24)

Hemoglobin concentration and reticulocyte count The hemoglobin concentration was mea

Table 25 Number of patients with abnormal values in the routine tests of hemostasis. Some f the first hospitalized patients were not examined with all tests. The number of tested patients are presented in the table Description of test occasions is presented in chapter 2, methods and reference values in chapter 3 II

Method	tested	Number of patients with abnormal values only first occasion	both first and second occasion	only second occasion	t least no occasion
All routine tests	151				64 (41 %)
Capillary fraglity	135	14	5	–	19 (15 %)
Platelet count	149	6	7	–	13 (9 %)
Bleedi g time	139	19	1	–	20 (15 %)
Blood clotting tests	151				35 (23 %)
Fibrinogen	143	3	0	0	3
Simplastin A	151	10	6	2	18
APTT	144	4	3	1	8
Faktor VIII	144	5	4	4	13

history of epistaxis in a significantly higher frequency than the other patients. The frequency of abnormality in one or more of the routine tests of hemostasis was not higher in patients with a family history of epistaxis than in the other patients, indicating that it might be localized defects in the nasal vessels that are inherited.

The frequency of abnormal values in routine tests of hemostasis was not higher in the habitual bleeders than in the other patients indicating that habitual bleedings also might be due to localized defects in the nasal vessels.

It is impossible to conclude whether any of the different diseases observed in the patients were predisposing to occasional epistaxis. In patients with macroglobulinemia Waldenström, Morbus Osler and some nasal diseases it is reasonable to anticipate a predisposition for habitual bleedings.

The laboratory methods used to detect potent acute bacterial infections were found to be poor indicators. This was obvious from the fact that only four of ten patients with clinically diagnosed acute sinusitis showed laboratory signs of a potent acute bacterial infection. With these methods it was thus impossible to separate viral upper respiratory infections from potent acute bacterial upper respiratory infections. The reason for such a separation also disappeared when it was shown in the histological study of the nasal mucosa (chapter 4 D) that severe inflammatory reactions in the nasal mucosa were observed in patients without histories of upper respiratory infections.

The frequency of abnormal transaminase values was significantly higher in male patients between 40 and 59 years old than in a population sample consisting 54 years old men. Men in this age group with abnormal transaminase values might be predisposed to occasional nose bleedings. The highest frequency of abnormal transaminase values was observed in patients assumed to be alcoholics indicating that it was abuse of alcohol that gave the abnormal transaminase values in some of the patients. There are however many other diseases which might give abnormal values of transaminases. No search for such diseases was carried out.

The frequency of patients with defects in the hemostasis have been studied by other investigators (table 1). Laeber and Heinrich (1960) observed that 75 per cent and Maurer and Ruhl (1965) noted that 100 per cent of the examined patients had defects in the hemostasis. When the patients in this study were tested with routine tests of hemostasis it was found that 41 per cent of the patients had defects in the hemostasis.

Acetylsalicylic acid irreversible impair platelet aggregation (Cronberg et al 1970). The normal survival time of platelets is ten days and as little as 0.5 g (one tablet) of acetylsalicylic acid may cause disturbed platelet function and impair the primary hemostasis for several days. The effect of the impaired platelet function can be studied by measuring the bleeding time.

As mentioned in chapter 4 D the frequency of histories of intake of acetylsalicylic acid was significantly higher in patients with epistaxis than in the population sample. When the effect of acetylsalicylic acid on the platelets was studied, it was found that all patients with prolonged bleeding time (Duke) and normal platelet count had taken acetylsalicylic acid some time during the previous week. It was also possible to demonstrate that the bleeding time was significantly longer in patients who had taken acetylsalicylic acid than in the other patients. That acetylsalicylic acid might give prolonged bleeding time has been previously shown by Weiss et al (1968), Mielke et al (1969).

When the patients were treated they had already bled during different long periods of time. The exact blood loss during the bleeding period was thus difficult to estimate. When the hemoglobin concentration was determined 2 to 4 days after the bleeding was finally arrested hemoglobin values less than the reference values were found in 43 per cent of the out patients and 73 per cent of the hospitalized patients. Most patients had an increase of reticulocyte count 4 to 8 days after the bleeding was finally arrested indicating that the measured low hemoglobin values were associated with the actual bleeding. As a consequence of the high frequency of low hemoglobin values the risk of getting sideropenia must be stressed and iron therapy recommended.

There has been reported a higher frequency of blood type O in patients with bleeding tendency than in other patients (Kornan-Bengtsen et al 1972).

No corresponding association between blood type and epistaxis was noted in the hospitalized patients in this study. A reason for this might be that the number of patients studied was too small.

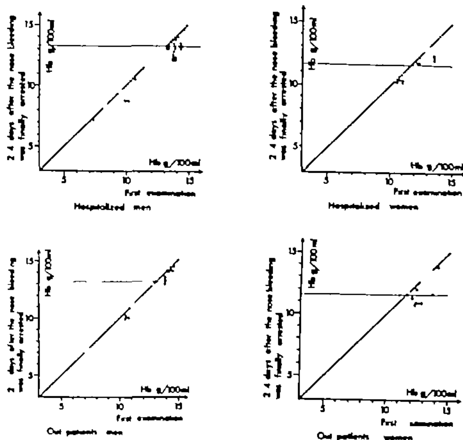


Figure 25 26 27 and 28 Hemoglobin concentration in g/100 ml.

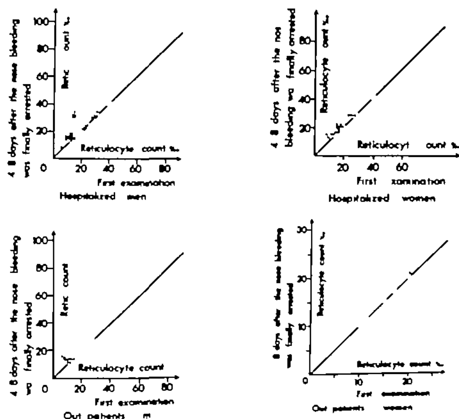


Figure 29 30 31 and 32 Reticulocyt count in ⁰/oo of total erythrocytes.

history of epistaxis in a significantly higher frequency than the other patients. The frequency of abnormality in one or more of the routine tests of hemostasis was not higher in patients with a family history of epistaxis than in the other patients, indicating that it might be localized defects in the nasal vessels that are inherited

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No corresponding association between blood type and epistaxis was noted in the hospitalized patients in this study. A reason for this might be that the number of patients studied was too small

Conclusions

Family histories of epistaxis were correlated to habitual bleedings but not to demonstrable defects in the hemostasis Neither were habitual bleedings correlated to demonstrable defects in the hemostasis.

In 41 per cent of the patients abnormal values *in at least one of the routine tests of hemostasis* were observed.

The bleeding time was significantly longer in patients who had taken acetylsalicylic acid than in the other patients. All patients with normal platelet count and abnormal bleeding time had *taken acetylsalicylic acid*

The measured hemoglobin values indicated that 43 per cent of the out patients and 73 per cent of the hospitalized patients were anemic.

H. Fibrinolytic activity in bacterial strains

The presence of fibrinolytically active bacterial strains in the nose and throat in patients with epistaxis have not earlier been reported If such strains could be isolated when the patients bled their presence might be an alternative explanation of repeated epistaxis

The extensively examined patients" (chapter 2) were studied with the following methods bacterial isolation (chapter 3 E) and a method for determination of fibrinolytic activity in bacterial strains (chapter 3 I)

Results

Bacterial strains. In 135 of the bleeding patients samples for bacterial growth were taken from the nose and throat when the patients bled In 36 patients (27 %) strains of staphylococcus aureus or beta-hemolytic streptococci were *isolated*

After two to three week a second sample was taken from all patients. This time strains of staphylococcus aureus or beta hemolytic streptococci were isolated from 22 patients. Altogether 46 patients had strains of staphylococcus aureus or beta hemolytic streptococci when they were bleeding and/or some weeks later (table 28)

From these 46 patients were thus isolated 53 strains of staphylococcus aureus and 11 strains of beta-hemolytic streptococci *All these 64 bacterial* strains were tested for fibrinolytic activity

Before the strains were tested the bacterial growth was estimated by registration of the turbidity in the culture The optical density in the cultures varied between 0 34 and 1 15 In 57 of *the cultures the optical density was 0 71 to 1.0*

Fibrinolytic activity The fibrinolytic activity of the strains from 46 patients was tested. It was found that 12 patients had strains with fibrinolytic activity Only four of these patients had had an upper respiratory infection during the previous week. From 9 patients fibrinolytic strains were only isolated when the patients had epistaxis. From 2 patients fibrinolytic strains were isolated during the epistaxis period as well as some weeks later *One patient had a fibrinolytic strain only* when he was examined some weeks after the bleeding. Unfortunately no samples were taken for bacterial cultivation when this patient had epistaxis.

Fibrinolytic activity was found in 6 strains of staphylococcus aureus and in 6 strains of *beta hemolytic streptococci (table 29) In 6 of* these patients the isolated strains must be regarded as fibrinolytically highly potent as the activity was equally high as that of a streptococcal strain usually employed in the production of streptoki nase for commercial purposes

In one experiment the relation between *bacterial growth and registered fibrinolytic* activity was studied in the reference strain When the growth as indicated by the optical density was

Table 28. Number of patients with bacterial strains of staphylococcus aureus (st.a.) and beta-hemolytic streptococci (h.str.)

	Number of patients with			
	st.a.	h.str.	st.a. + h.str	One or more strain
Only when the patients bled (I)	20	2	2	24
Only some week later (II)	9	1	0	10
On both occasions (I + II)	9	1	2	12

within the limits of the tested strains no definite difference in fibrinolytic activity was observed.

Comments

In 11 patients (8 per cent of all tested patients) fibrinolytically active bacterial strains were found when the patients bled.

A fibrinolytic bacterial strain present in the nose of a patient with epistaxis produces kinase which might dissolve formed blood clots in ruptured nasal vessels. In this way the bleeding might start again. The split products of the fibrinolysis might also inhibit new clot forming (Kowalski 1968).

Although only few fibrinolytic bacterial strains were found their presence illustrates the possibility that fibrinolytically active bacterial strains might be involved in the hemostasis of epistaxis.

Conclusion

During the bleeding period fibrinolytically active bacterial strains were found in 8 per cent of all examined patients with epistaxis. In 4 per cent of all patients the fibrinolytic strains were highly potent. The presence of such bacterial strains might be an alternative explanation of repeated epistaxis.

I. Fibrinolytic activity in euglobulin precipitate from blood plasma

The spontaneous fibrinolytic activity in blood is increased after emotional stress (Fearnley 1965). It is a common clinical observation that patients with epistaxis are upset, scared and frightend owing to the bleeding from the nose. This emotional stress might increase the spontaneous fibrinolytic activity in blood.

In this study the spontaneous fibrinolytic activity in euglobulin precipitate from plasma was measured in nose bleeding patients when they bled and some weeks later. The fibrinolytic activity releasable from the vessel wall after venous occlusion was also studied in patients with epistaxis as well as in control subjects.

Study groups. The spontaneous fibrinolytic activity was studied in 45 patients. Two examinations were carried out, the first when the patient was bleeding and the second 9 to 30 days later. In 10 patients the spontaneous fibrinolytic activity was followed with repeated tests.

Table 29. Fibrinolytic activity in bacterial strains found in the examined patients.

Patients number	Age	Sex	Histories of ASA	URI	Duration of epistaxis (hours)	When the patients bled: Bacterial isolation from Nose	Throat	Fibrinolytic activity in strains from Nose	Throat	Some weeks later: Bacterial isolation from Nose	Throat	Fibrinolytic activity in strains from Nose	Throat
9	68	man			214	h str st	normal	++ 0		normal	normal		
33	63	man			88	h str	h str	+++	+++	normal	normal		
34	63	woman			57	st	st a.			normal	normal		
39	61	man			192	st a.	normal			normal	normal		
50	57	man			48	st	st a.	+++	+++	normal	normal		
[illegible]	44	man			24	h str	h str			st a.	st a.	0	0
91	41	woman			72	no samples taken				normal	h str		+++
113	22	woman			2	st a.	normal	++++		normal	normal		
116	21	man			32	st a.	normal	+++		st a.	normal	+++	
120	15	man			6	no growth	h str		+++	no growth	h str		+++
152	72	man			24	st a.	normal	+++		normal	normal		
132	71	man			96	st a. h str	st a. h str	0	0	normal	normal		

Normal bacterial isolation means that no potentially pathological bacterias are isolated.
st staphylococcus aureus
h str hemolytic streptococcy
ASA acetylsalicylic acid
URI upper respiratory infection

The fibrinolytic activity in euglobulin precipitate from plasma after venous occlusion was studied in 12 patients selected at random during the autumn 1971 (Table 30). Two examinations were performed the first when the patients bled from the nose and the second one month later

To serve as a control group 12 healthy subjects of the same sex and about the same age as the patients were tested with venous occlusion tests (table 30)

Methods The fibrinolytic activity in euglobulin precipitate from plasma was determined according to the method described in chapter 3 K. All patients were tested between 9 and 12 a m

The *fibrinolytic capacity* of the vessel wall means the fibrinolytic activity in resuspended euglobulin precipitate after venous occlusion (Robertsson et al 1971)

The difference in mm^2 lysis area between the fibrinolytic activity in resuspended euglobulin precipitate after venous occlusion and the spontaneous fibrinolytic activity before venous occlusion is called the *releasable blood activity*

Statistical analyses The patients and the controls were divided into four homogenous subgroups with regard to sex and age in order to avoid the influence of sex and age in the correlations The statistical analyses were performed with Fisher s test within each group (Oden and Wedel 1973) The results of the subgroups were then pooled by a special technique (Oden and Wedel 1974) to get a general conclusion about the correlations in the study groups. A difference between the study groups is regarded as significant when $p < 0\ 05$

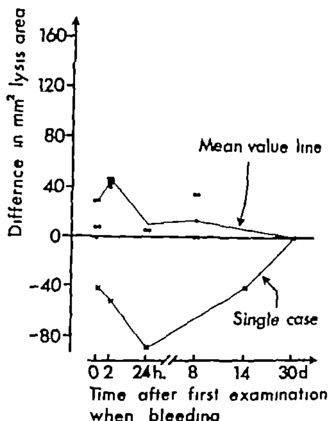


Figure 34 Spontaneous fibrinolytic activity in 10 patients followed by repeated tests. In each patient the value determined one month after the actual bleeding was regarded as resting value and marked with zero. The differences in lysis area between the resting value and the values measured on the other test occasions were calculated and are presented as dots in the figure. The mean values of the different test occasions are connected in the figure One patient whose reactions differed from the other patients is marked separately

Results

Spontaneous fibrinolytic activity In 45 patients tested the fibrinolytic activity was significantly higher ($p < 0.001$) when the patients bled compared with some weeks later (figure 33)

In 8 patients followed with repeated tests the fibrinolytic activity was higher when the patients bled than one month later In one patient the fibrinolytic activity was equal on both occasions (figure 34) When the values of these 9 patients were followed after the actual bleeding it was noted that the fibrinolytic activity had increased after 2 hours and decreased after 24 hours

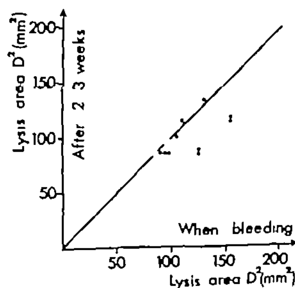


Figure 33 Spontaneous fibrinolytic activity in 45 patients with epistaxis when bleeding and 2–3 weeks late

There was no difference in the spontaneous fibrinolytic activity between 12 patients (in whom venous occlusion tests were also performed) one month after the actual bleeding and 12 control subjects (Table 30).

Fibrinolytic activity after venous occlusion. The releasable blood activity was significantly higher in the patients one month after the actual bleeding (when they were resting) than in the control subjects. (figure 35).

When the releasable blood activity determined at the first examination of the patients, was correlated to the duration of the nose bleeding the following was observed. Among the seven patients, who had bled less than four hours before the first examination, the releasable blood activity was significantly lower when the patients bled than one month later (figure 35).

Among the remaining five patients, who had bled more than six hours before the first examination the releasable blood activity was higher when the patients bled than one month later (figure 35).

Comments

It is known that the spontaneous fibrinolytic activity in blood has a diurnal variation (Fearnley 1965). All examinations in this study were performed between 9 and 12 a.m. in order to exclude these diurnal variations.

Most likely the increase of spontaneous fibrinolytic activity when bleeding and 2 hours later is explained by emotional stress in association with the bleeding and probably also stress owing to the blood loss.

The fibrinolytic activity releasable from the vessel wall after venous occlusion was measured and correlated to the duration of the nosebleeding. All patients who had bled less than 4 hours could release less fibrinolytic activity when they bled than when they were controlled after one month. As a hypothesis it might be assumed that the releaseable activity in these patients was evacuated. Patients who had bled more than six hours could release more fibrinolytic activity when they bled than after one month. The reason of this is unknown.

Conclusions

In patients with epistaxis the spontaneous fibrinolytic activity in euglobulin precipitate from plasma was significantly higher when the patients bled than some weeks later.

The releasable fibrinolytic activity from the

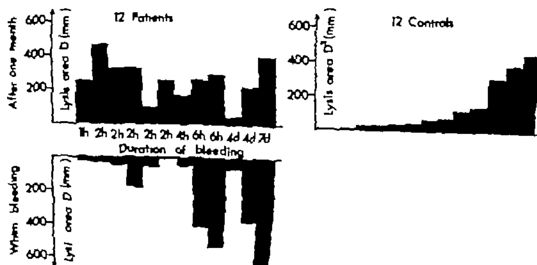


Figure 35. The releasable fibrinolytic activity from the vessel wall after venous occlusion. The patients are presented in sequence according to the duration of the nose bleeding. The height of the upturned staples show the activity after one month (resting values) and the downturned bars the activity when bleeding. The controls are presented in sequence according to the value of the activity.

The fibrinolytic activity in euglobulin precipitate from plasma after venous occlusion was studied in 12 patients selected at random during the autumn 1971 (Table 30). Two examinations were performed the first when the patients bled from the nose and the second one month later

To serve as a control group 12 healthy subjects of the same sex and about the same age as the patients were tested with venous occlusion tests (table 30)

Methods The fibrinolytic activity in euglobulin precipitate from plasma was determined according to the method described in chapter 3 K All patients were tested between 9 and 12 a m

The *fibrinolytic capacity* of the vessel wall means the fibrinolytic activity in resuspended euglobulin precipitate after venous occlusion (Robertsson et al 1971)

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Statistical analyses The patients and the controls were divided into four homogenous subgroups with regard to sex and age in order to avoid the influence of sex and age in the correlations The statistical analyses were performed with Fisher s test within each group (Oden and Wedel 1973) The results of the subgroups were then pooled by a special technique (Oden

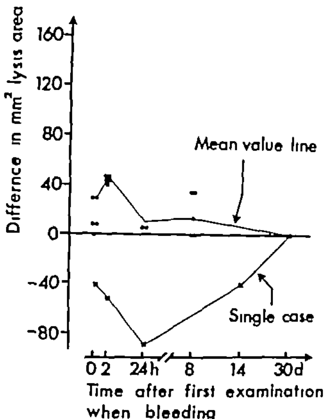


Figure 34 Spontaneous fibrinolytic activity in 10 patients followed by repeated tests. In each patient the value determined one month after the actual bleeding was regarded as resting value and marked with zero. The differences in lysis area between the resting value and the values measured on the other test occasions were calculated and are presented a dots in the figure Th mean values of the different test occa ions are connected in the figure One patient whose reactions differed from the other patients is marked separately

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In 8 patients followed with repeated tests the fibrinolytic activity was higher when the patients bled than one month later In one patient the fibrinolytic activity was equal on both occasions (figure 34) When the values of these 9 patients were followed after the actual bleeding it was noted that the fibrinolytic activity had increased after 2 hours and decreased after 24 hours

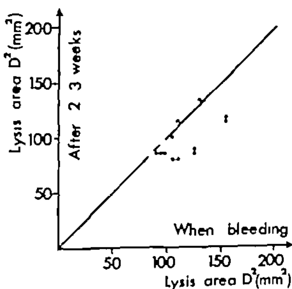


Figure 33. Spontaneous fibrinolytic activity in 45 patients with epistaxis when bleeding and 2–3 weeks lat r

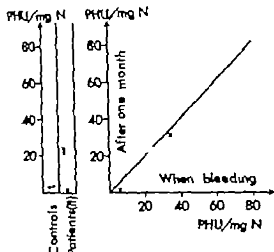


Figure 36. Total fibrinolytic activity in the nasal mucosa. The values of 12 patients with epistaxis (x) when bleeding (I) and one month later (II). The values of 12 control subjects ( ).

acid stable fibrinolytic activity as PHUa per mg nitrogen of the nasal mucosa.

The statistical analyses were performed as described in chapter 4 L. A difference is regarded as significant when $p < 0.05$

Results

Total fibrinolytic activity. In the 12 patients the total fibrinolytic activity in the nasal mucosa was

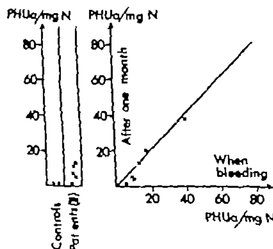


Figure 37. Acid stable fibrinolytic activity in the nasal mucosa. The values of 12 patients with epistaxis (x) when bleeding (I) and one month later (II). The values of 12 control subjects ( ).

significantly higher when the patients bled than one month later. There was no significant difference between the control group and the patients one month after the actual bleeding (figure 36).

Acid stable fibrinolytic activity. In the 12 patients the acid stable fibrinolytic activity in the nasal mucosa was higher when the patients bled than one month later. The difference was however not significant. There was no significant difference between the control group and the patients one month after the actual bleeding (figure 37).

Comments

The higher total fibrinolytic activity in the nasal mucosa when the patients bled from the nose compared with one month later might be either a localized phenomenon in the nasal mucosa or it might be a recorded sign of a generalized increase of tissue activity when the patients were bleeding.

Todd (1959) showed that the fibrinolytic activity in the tissue was localized in endothelial cells. Fearnly (1965) suggested that the blood activator was derived from the venous endothelium and that the venous system had an active secretory function. Nilsson et al (1969) supposed that the tissue activator was released in a labile form into the blood stream.

A high fibrinolytic activity in the nasal mucosa during the bleeding period might thus result in a high local activity in the blood stream and give a too quick dissolution of blood clots in the nasal vessels.

Conclusion

The total fibrinolytic activity in the nasal mucosa was significantly higher in patients with epistaxis when they bled compared with one month later. This increase of total fibrinolytic activity when bleeding might be of importance as an explanation of recurrent nose bleedings.

L. A double blind study to evaluate the effect on epistaxis with oral administration of the antifibrinolytic drug tranexamic acid (Cyklokapron®)

In order to study the effect of an antifibrinolytic drug on recurrent nose bleedings a double blind study with tranexamic acid (Cyklokapron®) was performed on hospitalized patients with epistaxis.

vessel wall after venous occlusion was significantly higher in the patients, one month after the bleeding episode than in the control subjects.

K. Fibrinolytic activity in the nasal mucosa

The fibrinolytic activity in the nasal mucosa has been studied by Buch Rasmussen (1966). When the fibrinolytic activity in the nasal mucosa from two patients with epistaxis, was compared with the activity in the mucosa from five control subjects no difference in fibrinolytic activity was found

In this study patients with epistaxis were studied when bleeding and one month later The purpose was to investigate whether the fibrinolytic activity in the nasal mucosa was changed when the patients bled

The fibrinolytic activity in the patients was also compared with the activity in control subjects in order to study if the patients differed from the control subjects.

Study groups. The fibrinolytic activity in the nasal mucosa was studied in 12 patients selected at random during the autumn 1971 (table 31) Two examinations were performed on each patient the first when the patient was bleeding and the second one month later

To serve as a control group 12 healthy subjects of the same sex and about the same age as the patients were examined (table 31)

Methods. The fibrinolytic activity in the nasal mucosa was determined according to the method presented in chapter 3 L. All examinations were performed between 9 and 12 a.m. A small piece of nasal mucosa was taken without anaesthesia from the anterior part of the inferior concha. In the patients the two biopsies were taken from the nasal cavity opposite to the bleeding, some mm apart from each other The biopsies were immediately frozen to −20°C and kept frozen until they were analysed

The total fibrinolytic activity is presented as PHU per mg nitrogen of the nasal mucosa and the

Table 30 Fibrinolytic activity in euglobulin precipitate in plasma (lysis area in mm²)

Patients number	Age	Sex	Duration of bleeding	Spontaneous fibrinolytic activity		Fibrinolytic capacity		Releasable activity	
				when bleeding	after 1 month	when bleeding	after 1 month	when bleeding	after 1 month
7	71	man	1 hour	100	97	119	346	19	249
10	70	man	2 hours	97	86	124	563	27	477
110	26	woman	2 hours	06	135	255	457	49	322
111	25	man	2 hours	156	123	339	449	183	326
115	22	woman	hours	87	65	148	162	61	97
134	79	man	2 hours	78	118	83	375	5	257
49	70	man	4 hours	152	190	201	359	49	169
37	64	woman	6 hours	204	127	508	382	404	255
45	60	man	6 hours	155	105	670	398	515	293
40	60	woman	4 days	136	107	200	153	64	46
70	53	man	4 days	110	99	472	318	362	219
18	67	man	7 days	129	94	740	483	611	389
Control subjects									
A	73	man		55		85		30	
B	72	man		115		495		380	
C	23	woman		100		105		5	
D	30	man		50		95		45	
E	21	woman		65		100		35	
F	79	man		170		615		445	
G	77	man		120		240		120	
H	71	woman		155		220		65	
I	62	man		135		275		140	
K	57	woman		145		450		305	
L	54	man		140		215		75	
M	62	man		85		110		25	

he received the bottle with his number and was told to take the tablets as in the hospital.

The dosage was 1 g three times a day. Later investigations on for example conization operations (Rybo and Westerberg 1972) have shown that a dosage of 1.5 g three times a day is preferable when the fibrinolytic activity is to be inhibited.

The tampons in the nose were taken away according to a previously made time table. The water in the Foley catheter balloon was drained 12 to 24 hours after the bleeding had stopped. The catheter was taken away 3 to 6 hours later. If no bleeding occured within 12 to 24 hours the anterior gauze tampon was taken away until fresh blood appeared on the gauze. Every 3 to 6 hours, except during the night, the gauze was taken away until all was out. The patient was sent home 12 to 24 hours later on the following morning.

When a new severe bleeding occured a new posterior and/or anterior tampon was given. These tampons were taken away as previously described.

In other investigations on Cyklokapron® it has been possible to evaluate the effect of treatment by measuring the blood loss (Nilsson and Rybo 1967, Hedlund 1970). In this study it was not possible to evaluate the effect of Cyklokapron® by measuring the blood loss as the patients swallowed a part of the blood they lost.

The effect of the therapy was instead evaluated by using a point scale. When the treatment had begun the severity and the number of recurrent bleedings were registered and given bleeding points. In each patient the bleeding points for the ten days of treatment were then added and presented as total amount of bleeding points.

The recurrent bleedings, which occurred within intervals of twelve hours during the ten days of treatment, were classed twice a day and given the following bleeding points: 0 = no bleeding, 1 = unimportant bleeding, 2 = small bleeding during some minutes, not treated, 4 = repeated small bleedings, not treated, 6 = large bleeding which required local treatment (tampons).

Whether the bleeding was large and requiring new tampons or not, was in daytime determined by the author and at other times by the emergency ENT-doctor at the clinic. One to three days after the drug treatment was finished the patients visited the hospital again. They were examined and

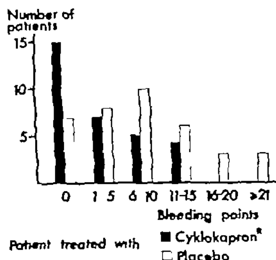


Figure 38. Number of patients with different bleeding points.

questioned whether any bleedings from the nose had occurred during the treatment at home.

The hospitalisation time was used as another criterea on the effect of the treatment. The hospitalisation time depended on whether new bleedings occurred, how quickly the tampons could be taken away and whether new tampons had to be used.

The statistical analyses were performed with contingency tables. All the significances which are presented are at a level $p < 0.01$.

Results

The total amount of bleeding points in each patient was significantly less in patients who received Cyklokapron® than in the patients who received placebo (figure 38).

When the total amount of bleeding points in the two groups of patients were calculated a *significant difference* was found between the two groups of patients (table 33).

The number of patients with at least one recurrent bleeding after the therapy had started and after the third day of treatment was significantly less in the Cyklokapron® than in the placebo group (table 34).

After the third day of treatment only two patients who received Cyklokapron® had a recurrent bleeding each. One patient had a small

Study group All patients who were hospitalized due to epistaxis from february to december 1971 (at the ENT-clinic Göteborg) were selected for this double blind study Cyklokapron was given to 31 patients and placebo to 37 patients.

The patients who were treated with Cyklokapron® and the patients who received placebo did not differ with regard to histories of upper respiratory infections, intake of acetylsalicylic acid and hypertension (table 32) The mean age in the two groups was the same as well as the localisation of the bleeding source and the local treatment primarily given

Methods. When the patients came to the hospital the bleeding was arrested with a posterior Foley catheter and/or anterior gauze tampons (chapter 3 C) After the bleedings were arrested the patients were hospitalized.

Assignment of Cyklokapron® tablets of placebo tablets was performed by random numbers and the labels of the bottles bore only the patients serial number (1 2 etc) The administration of tablets began within one hour after hospitalisation. The patients were given Cyklokapron® or placebo during ten days. When a patient left the hospital

Table 32. Presentation of the patients in the double blind study

	Patients treated with Cyklokapron®	Placebo
Number of patients in the group	31	37
Age in years (mean and S D.)	56 ± 17	56 ± 17
Habitual bleeders	5	5
Histories of		
Upper respiratory infections	16 (52 %)	19 (51 %)
Intake of acetylsalicylic acid	21 (68 %)	26 (70 %)
Hypertension	9 (29 %)	9 (4 %)
Localisation of the bleeding source		
Visible	11	19
Invisible	20	18
Local treatment		
Anterior gauze tampons	15	17
Posterior Foley chatheter and anterior gauze tampons	15	18
None	1	2

Table 31 Fibrinolytic activity in the nasal mucosa.

Patients number	Age	Sex	Duration of bleeding	Total activity PHU/mgN when bleeding	Total activity PHU/mgN after 1 month	Acid stable activity PHUa/mgN when bleeding	Acid stable activity PHUa/mgN after 1 month
7	71	man	1 hour	17	22	4 0	11
10	70	man	2 hours	23	23	13	13
110	6	woman	2 hours	48	30	26	13
111	25	man	2 hours	25	3	17	24
115	22	woman	2 hours	30	25	20	9
134	79	man	2 hours	27	24	14	9
49	70	man	4 hours	60	15	40	7
37	64	woman	6 hours	72	57	40	38
45	60	man	6 hours	23	18	7.5	4 7
40	60	woman	4 days	18	9	10	3.6
70	53	man	4 days	5 5	1 0	4 0	0 7
18	67	man	7 days	34	31	19	20
Control subjects							
A	73	man		15		6	
B	72	man		20		10	
C	23	woman		2.1		1.6	
D	30	man		20		13	
E	21	woman		27		17	
F	79	man		90		71	
G	77	man		50		47	
H	71	woman		24		23	
I	62	man		2.7		1.3	
K	57	woman		24		14	
L	54	man		15		11	
M	62	man		50		38	

he received the bottle with his number and was told to take the tablets as in the hospital.

The dosage was 1 g three times a day. Later investigations on for example conization operations (Rybo and Westerberg 1972) have shown that a dosage of 1.5 g three times a day is preferable when the fibrinolytic activity is to be inhibited.

The tampons in the nose were taken away according to a previously made time table. The water in the Foley catheter balloon was drained 12 to 24 hours after the bleeding had stopped. The catheter was taken away 3 to 6 hours later. If no bleeding occured within 12 to 24 hours the anterior gauze tampon was taken away until fresh blood appeared on the gauze. Every 3 to 6 hours, except during the night, the gauze was taken away until all was out. The patient was sent home 12 to 24 hours later on the following morning.

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In other investigations on Cyklokapron® it has been possible to evaluate the effect of treatment by measuring the blood loss (Nilsson and Rybo 1967, Hedlund 1970). In this study it was not possible to evaluate the effect of Cyklokapron® by measuring the blood loss as the patients swallowed a part of the blood they lost.

The effect of the therapy was instead evaluated by using a point scale. When the treatment had begun the severity and the number of recurrent bleedings were registered and given bleeding points. In each patient the bleeding points for the ten days of treatment were then added and presented as total amount of bleeding points.

The recurrent bleedings, which occurred within intervals of twelve hours during the ten days of treatment, were classed twice a day and given the following bleeding points: 0 = no bleeding, 1 = unimportant bleeding, 2 = small bleeding during some minutes, not treated, 4 = repeated small bleedings, not treated, 6 = large bleeding which required local treatment (tampons).

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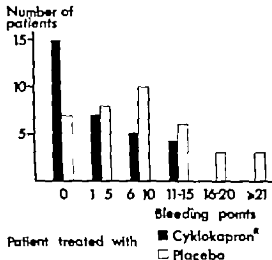


Figure 38. Number of patients with different bleeding points.

questioned whether any bleedings from the nose had occurred during the treatment at home.

The hospitalisation time was used as another criteria on the effect of the treatment. The hospitalisation time depended on whether new bleedings occurred, how quickly the tampons could be taken away and whether new tampons had to be used.

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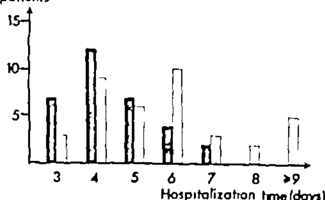
Results

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After the third day of treatment only two patients who received Cyklokapron® had a recurrent bleeding each. One patient had a small



Patients treated with: ■ Cyklocapron® 4.4 ± 1.1
Placebo 6.0 ± 2.5

Figure 39 Number of patients with different hospitalisation time

bleeding one day after leaving the hospital and one patient with delirium tremens had a severe bleeding in the hospital on the fourth day of treatment

The hospitalisation time was significantly shorter in the patients who were treated with Cyklokapron® than in those who received placebo (figure 39)

Diarrhoe abdominal pain, nausea and dizziness are mentioned as general side effects of Cyklokapron® (for example Nilsson and Rybo 1967 Andersson and Nilsson 1969).

Many patients in this study had lost a lot of blood before they came to the hospital and were in shock or preshock when examined before hospitalisation. In these patients it was difficult to evaluate general side effects of the treatment.

Table 33. Total amount of bleeding points in the two groups of patients. The bleeding point scale 1 unimportant bleeding 2 small bleeding during some minutes, not treated 4 repeated small bleedings, not treated 6 = large bleeding which required treatment with tampons

	Patients treated with Cyklokapron® Bleeding points				Placebo Bleeding points			
	1	2	4	6	1	2	4	6
Number of classified bleedings in the group								
Total	26	11	6	6	47	36	19	18
After 3 days therapy	0	1	0	1	18	19	3	7
After 5 days therapy	0	0	0	0	13	4	0	3

Table 34 Number of patients with at least one recurrent bleeding.

	Patients treated with Cyklokapron®	Placebo
Total	16 (52 %)	30 (81 %)
After 3 days therapy	2 (6 %)	15 (41 %)
After 5 days therapy	0	10 (27 %)

During the hospitalisation time none of the patients complained of symptoms which might be taken for general side effects. The most common complains were pains due to the nasal tampons.

Local side effects of the treatment were noted in two patients. One patient who received Cyklokapron® and one patient who received placebo had small synechies in the nose after the treatment was finished. Most probable these synechies depended on the local treatment with tampons.

Comments

From the scientific point of view it might have been preferable to use Cyklokapron® or placebo as the only therapy in this study It would, however not have been possible to justify this ethically Conventional local treatment had to be used together with Cyklokapron® and placebo

The tampons must be regarded as errors in the evaluation of the therapy effect. When the tampons were taken away or moved small bleedings sometimes started. These small bleedings were not registered

An explanation of some of the recurrent bleedings observed during the first three days of therapy might be that the tampons were moved by the doctor or the patient The recurrent bleedings during the first three days were however significantly less in the patients who received Cyklokapron® than in the other patients.

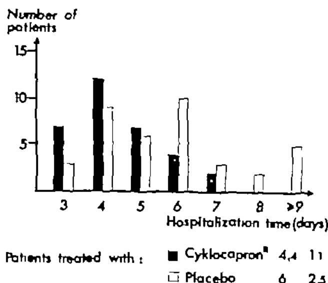
The effect of the therapy in this double blind study was evaluated by the severity and number of recurrent nose bleedings. The recurrent bleedings were classified according to a point scale There have not been any difficulties in determing what bleeding point the patients should have when they were hospitalized. In the period after hospitalisation it has also been possible to classify the recurrent bleedings without difficulties. As shown in the results the patients who were treated with Cyklokapron® had significantly less recurrent nose

bleedings both in severity and number than the patients who received placebo.

Conclusions

In this double blind study with the antifibrinolytic drug tranexamic acid (Cyklokapron®) it was possible to demonstrate that recurrent bleedings in patients with epistaxis were significantly less in number and severity when the patients were treated with Cyklokapron® compared with placebo

It was also observed that the hospitalisation time was significantly shorter when the patients were treated with Cyklokapron® instead of placebo.



Patients treated with: ■ Cyklocapron® 4,4 1 1
□ Placebo 6 2,5

Figure 39 Number of patients with different hospitalisation time

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The effect of the therapy in this double blind study was evaluated by the severity and number of recurrent nose bleedings The recurrent bleedings were classified according to a point scale. There have not been any difficulties in determing what bleeding point the patients should have when they were hospitalized. In the period after hospitalisation it has also been possible to classify the recurrent bleedings without difficulties. As shown in the results the patients who were treated with Cyklokapron® had significantly less recurrent nose

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It was also observed that the hospitalisation time was significantly shorter when the patients were treated with Cyklokapron® instead of placebo.

CHAPTER 5

GENERAL DISCUSSION

In the introduction four questions of practical clinical interest were presented

1 Why does a nose bleeding start?
2. What is predisposing to nose bleedings?
3 Why have some nose bleedings a long duration?
4 Why are some nose bleedings recurrent?

All the evidence necessary to give a complete answer to any of these questions are not yet available. The results of the present and of other investigations will however be used in an attempt to discuss the problems as far as possible

1 Why does a nose bleeding start?

A nose bleeding might start after a trauma against the nasal structures of that magnitude that at least one vessel ruptures or it might start "spontaneously"

In 28.5 per cent (322/1118) of the patients in the present investigation the nose bleeding started after different traumas against the nasal structures for example nose picking, nose blowing or a strike against the nose (chapter 4 B)

In 6 5 per cent (72/1118) of the patients the bleeding started in association with physical or psychical exhaustion. The releasing mechanism in these cases is difficult to estimate

In the remaining 65 per cent (724/1118) of the patients the nose bleeding started without any obvious reason

2. What is predisposing to nose bleedings?

a. Predisposing factors localized in the nasal mucosa. It has been shown by Naumann (1961) that inflammatory reactions which were chemically induced in the nasal mucosa of rabbits, caused vessel wall injuries.

In this clinical study nasal mucosa biopsies, taken from the nasal cavity opposite to the bleeding cavity were analysed histologically In all of ten patients with epistaxis histological signs of severe or moderate inflammatory reactions were observed in the nasal mucosa. In the same number of control subjects, without epistaxis, no or only slight histological signs of inflammatory reactions were observed in the biopsies (chapter 4 D). In five of the ten patients from whom nasal mucosa biopsies were taken the inflammatory reactions which were observed probably depended on upper respiratory infections.

A higher frequency of histories of upper respiratory infections was noted in patients with epistaxis than in a population sample (chapter 4 C).

Upper respiratory infections giving inflammatory reactions in the nasal mucosa might predispose to epistaxis if the infection results in vessel wall injuries.

Chemically induced inflammatory reactions in the nasal mucosa giving epistaxis have been observed as an epidemic occupational disease after daily work with gentian violet (Quinby 1968).

b. Predisposing factors localized in the vessel wall. Arteriosclerosis is mentioned by Hara (1962) as an etiological factor of epistaxis.

The walls of the nasal arteries have been studied histologically by Shaheen (1970) In aging individuals he observed a degeneration in the arterial wall characterized by loss of muscle in the tunica media and its replacement of collagen The degenerations were more pronounced in patients who had suffered from epistaxis than in other subjects.

Varicose veins on the nasal septum are sometimes observed in patients with epistaxis. Dohl-

mas (1938), who made serial sections of the nasal mucosa in patients without epistaxis, said that he sometimes found very wide superficial veins with a normal intima but only a very thin surrounding vessel wall. These pathological changes might predispose to a vessel rupture and nose bleeding.

Patients with Mb Osler who frequently have epistaxis, have pathological changes in the walls of small vessels, which usually contain only endothelial cells (Jahnke 1970).

It has not been systematically studied whether other nasal vessel wall defects than those found in patients with Mb Osler are inherited. In the present investigation it was observed that habitual nose bleeders had a family history of epistaxis in a higher frequency than other nose bleeders (chapter 4 G). It was also noted that the frequency of abnormality in any of the routine tests of hemostasis, were the same in patients with a family history of epistaxis as in the other patients (chapter 4 G). This speech in favour of the hypothesis that localized defects in the vessel walls of the nasal mucosa are inherited.

c. Predisposing factors due to blood flow and pressure. Long lasting abnormalities in blood flow and pressure in the nasal vessels of rabbits gave pathological changes in the vessel walls (Naumann 1961). It is difficult to evaluate to what extent changes in blood flow and pressure in a human nasal vessel might predispose to a vessel rupture. It is also unknown whether the nasal vessels with arteriovenous anastomoses, venous plexus and sinusoidal spaces (chapter 1 E) are more susceptible to changes in blood flow and pressure than other vessels.

Increased viscosity of the blood and impaired circulation in small vessels, giving thrombosis and hemorrhages in retinal veins was observed in patients with macroglobulinemia Waldenström (Spätter 1959). In this disease repeated spontaneous small nose bleedings are frequently noted (Leading article Brit Med J 1965).

Hypertension is mentioned as an etiological factor of epistaxis in several clinical studies about epistaxis (chapter 1 B). Shaheen (1970) and Weiss (1972) could, however not find any correlation between hypertension and epistaxis. The conclusions from the present study confirm their observations.

In chapter 4 E is shown that the frequency of histories of hypertension was not higher in our patients with epistaxis than in a population sample. When the blood pressure was measured in 155 patients with epistaxis it was found that the distribution of different blood pressures was the same in the patients group as in a population sample (chapter 4 F). The frequency of distinct arterial bleedings from the nose was the same in patients with a history of epistaxis as in other patients (chapter 4 E).

A temporary increase of the blood pressure might, however result in a vessel rupture. Such a temporary increase might partly explain the start of nose bleedings in association with physical or psychical exhaustion.

d. Predisposing factors due to impaired hemostasis. As mentioned in the review of the literature, epistaxis is a common symptom in different defects of the hemostasis (Nilsson 1971, Biggs 1972). These defects might be due to diseases as for example acquired thrombocytopenia, inherited defects of coagulation factors or treatment with different drugs as dicumarol, heparin, streptokinase or acetylsalicylic acid. It is assumed that subjects with severe defects are more predisposed to bleeding symptoms than subjects with mild defects.

The significance of acetylsalicylic acid as a predisposing factor of nose bleedings has not been systematically studied before.

A dosis of 0.5 g acetylsalicylic acid can impair the platelet aggregation during several days (Cronberg et al 1970). It was observed by Mielke et al (1968) that the bleeding time was significantly prolonged after consumption of acetylsalicylic acid. In this clinical study it was noted that the bleeding time (according to Duke) was significantly longer in patients who had taken acetylsalicylic acid, compared with other nose bleeding patients (chapter 4 G).

Croft and Wood (1967) showed that acetylsalicylic acid can give gastric bleedings. In 80 per cent of the subjects studied, who received aspirin was found a blood loss in the stool of 2 to 10 ml per day. In 10 per cent of the subjects the blood loss

was more than 10 ml per day A blood loss of less than 2 ml per day which was regarded as normal, was only observed in 10 per cent of the tested subjects.

Parry and Wood (1967) observed that 94 per cent (33/35) of the patients with acute gastric bleeding had taken aspirin during the previous week.

In patients with von Willebrand's syndrome who frequently have epistaxis, Quick (1968) observed that epistaxis in some patients started spontaneously after consumption of aspirin.

In the present investigation it was noted that patients with epistaxis had taken acetylsalicylic *acid in a significantly higher frequency than* subjects in a control group (chapter 4 C)

Subjects in a population sample who had bled from the nose the previous week, had taken acetylsalicylic acid when they had an upper respiratory infection in a significantly higher frequency than other subjects (chapter 4 C).

These clinical observations support the hypothesis that acetylsalicylic acid predisposes to nose bleedings.

3 Why have some nose bleedings a long duration?

Most cases of nose bleedings are arrested spontaneously In a population sample 60 per cent of the subjects had had epistaxis at least once during lifetime but only 6 per cent of the subjects had *been treated for epistaxis by a doctor (chapter 4 A)*

There are different explanations of a long duration of a nose bleeding anatomical and physiological conditions in the nose changes in the functions of the vessel wall impaired form*ation of platelet plugs, impaired coagulation,* increased fibrinolysis and mechanical influences on the blood clot formation.

a. Anatomical and physiological conditions in the nose The vessel wall in subepithelial capillaries and small veins is thin and without muscular tissue (Messerklinger 1958). *These vessels are thus* supposed to lack ability of active contraction

According to Weddel et al (1945) large septal vessels, embedded in the mucosa, can not contract as easily as other vessels after laceration

b. Changes in the function of the vessel wall. In patients with Mb Osler the abnormal vessel walls do not contain any muscular layer (Jahnke 1970). The ability to vasoconstriction is lost in these abnormal vessels, which might give prolonged bleeding after vessel ruptures.

The prevention of petechial formation after capillary fragility tests is dependent upon the integrity of the capillary wall but also upon a normal platelet function In the present investigation abnormal capillary fragility was observed in 15 per cent (19/135) of the examined patients with epistaxis (chapter 4 G).

c. Impaired formation of platelet plugs. The bleeding time is a measure of the ability to form a *local platelet plug after a standardized skin inci*sion It was found that 15 per cent (20/138) of *the studied patients had abnormal bleeding time* indicating impaired platelet function (chapter 4 G)

The number of platelets was below the reference value in 9 per cent (13/149) of the patients examined (chapter 4 G)

d. Impaired coagulation. In other investigations impaired hemostasis were noted in one to a hundred per cent of the patients with epistaxis (chapter 1 B)

In this investigation it was found that 23 per cent (35/151) of the patients examined had impaired coagulation when tested with four diffe*rent routine coagulation tests* (chapter 4 G). It was *also noted that* 3 of 155 patients examined had taken dicumarol.

The split products after fibrinolysis impair blood clotting (Kowalski 1968 Larrieu et al 1972) The increased fibrinolytic activity in blood and nasal mucosa and the presence of fibrinolytically active bacterial strains in patients with epistaxis (chapter 4 H, I K) might result in split products capable of impairing the coagulation in nose bleeding patients.

e Mechanical influences on the blood clot formation. During clot formation after vessel ruptures in the nose movements of the nasal mucosa (and the immature clot) might interfere with the clot formation These movements can be due to breathing through the nose nose blowing, sneezing, a finger or a piece of cotton introduced into the bleeding nasal cavity

4. Why are some nose bleedings recurrent?

In many patients with epistaxis the nose bleeding starts again spontaneously some hours to some days after it has been arrested. Explanations of these secondary released nose bleedings might be that the blood clot is moved away or locally dissolved. It is also possible that the bleeding comes from a new bleeding source.

a. Mechanical influences on the blood clot. The clot can be moved away due to breathing through the nose, etcetera. A newly formed blood clot or a weak blood clot due to impaired coagulation is probably more susceptible to mechanical influences. An increased blood flow or increased blood pressure might as well wash away the clot.

b. Dissolution of the blood clot. The dissolution of the blood clot depends on fibrinolysis. Fibrinolysis is an enzymatic break down of fibrin by plasmin. Plasminogen, which is a precursor to plasmin, can be activated to plasmin by different activator systems (chapter 1 F).

In the present investigation three different plasminogen activator systems were studied: bacterial activator, blood activator and tissue activator in the nasal mucosa. The significance of these activator systems in patients with epistaxis have hitherto not been systematically studied.

I. *Fibrinolytic activity in bacterial strains.* From eleven of 135 examined patients with epistaxis (8 %) bacterial strains with ability to produce streptokinase or staphylokinase were isolated during the nasal bleeding (chapter 4 H). In these patients it seems reasonable to assume that the fibrinolytically active bacterial strains had dissolved blood clots in the nose and thus released recurrent bleedings.

II. *Fibrinolytic activity in the blood.* In this clinical study the spontaneous fibrinolytic activity in the plasma was measured in 45 patients (chapter 4 I). The fibrinolytic activity was found to be significantly higher when the patients were bleeding than some weeks later. A high activity during the bleeding period might dissolve blood clots in the nose quickly.

It was also observed that the fibrinolytic activity releasable from the vessel wall after venous occlusion was significantly higher in 12 patients, examined one month after the nose bleeding, than in 12 control subjects (chapter 4 J). A high ability to release fibrinolytic activity might give an increased activity in the blood during the bleeding period and result in a quick dissolution of formed blood clots.

III. *Fibrinolytic activity in the nasal mucosa.* With the aid of a new method for determination of tissue plasminogen activator in small pieces of nasal mucosa (chapter 3 L) the fibrinolytic activity was measured in 12 patients with epistaxis.

The total fibrinolytic activity in the nasal mucosa was significantly higher when the patients were bleeding than one month later (chapter 4 K). This increased fibrinolytic activity could upset the hemostatic balance and give a too quick dissolution of formed blood clots which might result in a recurrent nose bleeding.

Recently it has been reported by Kwaan and Silverman (1973) studying patients with Mb Osler that the fibrinolytic activity was higher in telangiectatic small vessels than in normal vessels in the patients. This finding suggest a role of fibrinolysis in patients with Mb Osler.

IV. *Inhibition of fibrinolytic activity.* In order to investigate whether an inhibition of fibrinolysis would decrease the number of recurrent nose bleedings a double blind study was performed with the antifibrinolytic *drug tranexamic acid* (Cyklokapron®). Those patients in whom the fibrinolytic activity was inhibited with Cyklokapron® had significantly less recurrent bleedings and less severe bleedings than patients treated with placebo (chapter 4 L).

The hospitalisation time was also significantly shorter in patients treated with Cyklokapron® compared with patients treated with placebo.

The results of this double blind study indicate that inhibition of fibrinolysis is of great importance to prevent recurrent epistaxis.

was more than 10 ml per day A blood loss of less than 2 ml per day which was regarded as normal was only observed in 10 per cent of the tested subjects.

Parry and Wood (1967) observed that 94 per cent (33/35) of the patients with acute gastric bleeding had taken aspirin during the previous week.

In patients with von Willebrand's syndrome who frequently have epistaxis Quick (1968) observed that epistaxis in some patients started spontaneously after consumption of aspirin.

In the present investigation it was noted that patients with epistaxis had taken acetylsalicylic acid *in a significantly higher frequency than* subjects in a control group (chapter 4 C).

Subjects in a population sample who had bled from the nose the previous week, had taken acetylsalicylic acid when they had an upper respiratory infection in a significantly higher frequency than other subjects (chapter 4 C)

These clinical observations support the hypothesis that acetylsalicylic acid predisposes to nose bleedings.

3 Why have some nose bleedings a long duration?

Most cases of nose bleedings are arrested spontaneously In a population sample 60 per cent of *the subjects had had epistaxis at least once during* lifetime but only 6 per cent of the subjects had *been treated for epistaxis by a doctor (chapter 4 A).*

There are different explanations of a long duration of a nose bleeding anatomical and physiological conditions in the nose changes in the functions of the vessel wall, impaired formation of platelet plugs, impaired coagulation, increased fibrinolysis and mechanical influences on the blood clot formation.

a. Anatomical and physiological conditions in the nose The vessel wall in subepithelial capillaries and small veins is thin and without muscular tissue (Messerkling 1958). These vessels are thus *supposed to lack ability of active contraction*

According to Weddel et al (1945) large septal vessels, embedded in the mucosa, can not contract as easily as other vessels after laceration

b. Changes in the function of the vessel wall. In patients with Mb Osler the abnormal vessel walls do not contain any muscular layer (Jahnke 1970). The ability to vasoconstriction is lost in these abnormal vessels, which might give prolonged bleeding after vessel ruptures.

The prevention of petechial formation after capillary *fragility tests is dependent upon the* integrity of the capillary wall but also upon a normal platelet function. In the present investigation abnormal capillary fragility was observed in 15 per cent (19/135) of the examined patients with epistaxis (chapter 4 G).

c Impaired formation of platelet plugs. The bleeding time is a measure of the ability to form a *local platelet plug after a standardized skin inc*ision. It was found that 15 per cent (20/138) of the studied patients had abnormal bleeding time indicating impaired platelet function (chapter 4 G)

The number of platelets was below the reference value in 9 per cent (13/149) of the patients examined (chapter 4 G)

d. Impaired coagulation. In other investigations impaired hemostasis were noted in one to a hundred per cent of the patients with epistaxis (chapter 1 B)

In this investigation it was found that 23 per cent (35/151) of the patients examined had impaired coagulation when tested with four different routine coagulation tests (chapter 4 G). It was also noted that 3 of 155 patients examined had taken dicumarol.

The split products after fibrinolysis impair blood clotting (Kowalski 1968 Larrieu et al 1972). The increased fibrinolytic activity in blood and nasal mucosa and the presence of fibrinolytically active bacterial strains in patients with epistaxis (chapter 4 H, I K) might result in split products capable of impairing the coagulation in nose bleeding patients.

e Mechanical influences on the blood clot formation. During clot formation after vessel ruptures in the nose movements of the nasal *mucosa (and the immature clot) might interfere* with the clot formation These movements can be *due to breathing through the nose nose blowing,* sneezing, a finger or a piece of cotton introduced into the bleeding nasal cavity

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SUMMARY

Bleedings from the nose are experienced by many people In spite of this the incidence the cause and course of nose bleedings have been poorly investigated.

In the present investigation a randomly selected population sample of 410 subjects and 1 118 patients, who visited Ear Nose Throat doctors due to epistaxis, were studied.

In the population sample was noted that 60 per cent of the subjects had bled from the nose at least once in life but only 6 per cent had been treated for it by a doctor

Subjects who frequently have nose bleedings do not necessarily require professional treatment.

The nose bleeding started without any obvious reason in 65 per cent of the patients, in 28 5 per cent it was released by different traumas against the structures of the nasal cavities.

The bleeding source was localized on the nasal septum in 91 per cent of the patients less than 20 years and in 68 per cent of the patients more than 40 years old.

Distinct arterial bleedings were more frequent in patients more than 40 years old than in younger patients.

Histories of upper respiratory infections and intake of acetylsalicylic acid were more common in patients with epistaxis than in subjects in the population sample About 10 per cent of the subjects in the population sample had noted an association between upper respiratory infections and nose bleedings.

In the patients, but not in the control subjects, inflammatory reactions in nasal mucosa biopsies, taken from the side opposite to the bleeding side were seen

The frequency of histories of hypertension was not higher in out patients than in the population sample. A history of hypertension did not seem to predispose to habitual nose bleedings.

The distribution of different blood pressures was the same in the examined patients (some weeks after the actual bleeding) as in a population sample

Family histories of epistaxis were correlated to habitual nose bleeding but not to demonstrable defects in the hemostasis. Neither were habitual bleedings correlated to demonstrable defects.

In 41 per cent of the patients examined abnormal values in at least one of the routine tests of hemostasis were observed. The bleeding time was significantly longer in patients who had taken acetylsalicylic acid than in the other patients. All patients with normal platelet count and abnormal bleeding time had taken acetylsalicylic acid.

The measured hemoglobin values indicated that 43 per cent of the out patients and 73 per cent of the hospitalized patients were anemic.

Fibrinolytically active bacterial strains were found in 8 per cent of all examined patients, when they were bleeding.

The spontaneous fibrinolytic activity in euglobulin precipitate from plasma was significantly higher when the patients bled than some weeks later

The releasable fibrinolytic activity from the vessel wall after venous occlusion was significantly higher in the patients, one month after the bleeding episode than in the control subjects.

With a new micro method for determination of tissue plasminogen activator it was found that the total fibrinolytic activity in the nasal mucosa was significantly higher when the patients bled compared with one month later

In a double blind study with the antifibrinolytic drug tranexamic acid (Cyklokapron®) it was possible to demonstrate that recurrent bleedings were significantly less in number and severity when the patients were treated with Cyklokapron® compared with placebo It was also observed that the hospitalisation time was significantly shorter when the patients were treated with Cyklokapron® instead of placebo

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APPENDIX

	Population sample							
	Men age group				Women age group			
	< 20	20–39	40–59	≥ 60	< 20	20–39	40–59	≥ 60
Number of subjects in the age group	42	51	48	49	42	54	56	68
with history of hypertension	0	3	1	13	1	4	7	33
treated for hypertension	0	0	1	9	0	1	6	26
with history of URI the previous week	19	13	14	11	20	17	18	11
ASA the previous week	9	11	15	8	12	23	27	26
URI and ASA	7	2	8	4	9	10	13	7
URI without ASA	12	11	6	7	11	7	5	4
ASA without URI	2	9	7	4	3	13	14	19
with no history of URI or ASA	21	29	27	34	19	24	24	38
Frequency of epistaxis								
Number of subjects who had								
never had bleeding	18	16	17	23	19	17	20	34
had single bleedings before	13	25	26	24	20	29	29	32
had single bleedings every year	5	7	3	2	2	6	5	0
had several bleedings every year	6	3	2	0	1	2	2	2
been treated for epistaxis at least once	0	7	0	4	0	5	3	5
had nose bleedings the previous 7 days	3	2	0	0	1	1	0	2
epistaxis associated to								
common cold	7	8	6	2	5	4	7	4
stress	3	9	7	2	3	10	5	1

ASA = acetylsalicylic acid
URI = upper respiratory infection

	Out patients							
	Men age group				Women age group			
	< 20	20–39	40–59	≥ 60	< 20	20–39	40–59	≥ 60
Number of subjects in the age group	143	118	145	174	101	55	84	187
with history of hypertension	1	3	27	37	0	0	11	69
treated for hypertension	–	–	–	–	–	–	–	–
with history of URI the previous week	106	70	72	62	64	28	35	57
ASA the previous week	65	58	77	96	46	28	52	96
URI and ASA	54	58	33	46	39	25	22	37
URI without ASA	5	12	39	16	25	3	13	[illegible]
ASA without URI	11	0	44	50	7	3	30	59
with no history of URI or ASA	6	48	29	62	30	24	17	69
Frequency of epistaxis								
Number of subjects who had								
first bleeding in life	12	14	40	33	9	5	19	38
had single bleedings before	50	34	75	93	29	22	41	91
had single bleedings every year	33	34	13	27	23	11	15	26
had several bleedings every year	48	36	17	21	40	17	9	32

	Hospitalized patients							
	Men age group				Women age group			
	< 20	20–39	40–59	≥ 60	< 20	20–39	40–59	≥ 60
Number of subjects in the age group	1	9	34	28	1	9	8	21
with history of hypertension	0	0	6	11	0	1	1	13
treated for hypertension	0	0	3	4	0	1	0	7
with history of URI the previous week	1	5	18	16	1	7	5	7
ASA the previous week	1	4	25	18	1	6	6	15
URI and ASA	1	4	15	13	1	5	5	4
URI without ASA	0	1	3	3	0	2	0	3
ASA without URI	0	0	10	5	0	1	1	11
with no history of URI or ASA	0	4	6	7	0	1	2	3
Frequency of epistaxis								
Number of subjects who had								
first bleeding in life	0	2	15	9	0	6	3	8
had single bleedings before	0	5	15	14	0	2	4	11
had single bleedings every year	0	0	2	4	0	1	0	1
had several bleedings every year	1	3	2	1	1	0	1	1

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BY

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SUPPLEMENT 321

Aural Participation in Congenital Malformations of the Organism

BY

GEORGE KELEMEN M.D

From the Eccles Temporal Bone Laboratory of the Ear Research Institute,
and the School of Medicine, University of Southern California,
Los Angeles, California, USA

UPPSALA 1974

Introduction

Aural manifestations that present themselves, not independently but as part of a more or less high degree of abnormality of the entire organism, have been termed by Marx (1926) secondary manifestations. They represent partial phenomena of general abnormalities. As to their time-distribution, or periods of origin, the following so-called teratological termination points can be placed (1) the end of the organogenetic phase roughly at the end of the third gestational month (2) at delivery· (3) during the post partum period without definite termination, when teratological influences may become manifest even at late phases of life.

Within all three periods, a number of cases were secured for further study with the aim to find, amid multiple malformations of the organism, aural participation—if any

Material and Methods

Opportunity for such study was offered in the substance of 54 cases with multiple malformations. Detailed clinical history autopsy protocol and sectional series of the temporal bones, of both sides, were extant. For the overwhelming majority the specimens were most obligingly released after autopsies at the Lying-In Hospital (pathologists Drs W Benirschke and S. G Driscoll), and the Children's Medical Center Hospital (pathologists Drs J M. Craig and G F Vawter) of the Harvard Medical School, Boston. Their cooperation, institutions and pathologists, are most heartily appreciated. The temporal bones were processed, after EDT (versene) decalcification, according to the usual celloidin method, sectioned, mostly in the horizontal plane and around 20 micra, stained with hematoxylin-eosin, Heidenhain-Mallory Bodian's, Gomori impregnation and, where warranted with auxiliary stains, and examined in direct and polarized light. Of these cases 26 originated from males 22 from females, in 6 the sex could not be ascertained. All three age groups, pre peri- and postnatal, were represented, in the following distribution

Period	No. of cases
Between 14 and 20 gestational weeks	4
Between 1 and 44 hours post partum	6
Between 3 days and 16 months post partum	35
Between 2 and 13 years of age	9

Four were stillborn craniotomy has been applied once, and one case carried the note neonatal death"

The ears turned out to be in the expected developmental stage and were without pathology in 21 cases (38.8%). It is regrettable that in the clinical history coming from departments without special interest in the condition of the hearing organ, no attention was paid to its functional history and data regarding hearing and vestibular function were lacking in patients of all ages.

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Findings

Table I demonstrates, in each case, separately the general malformation opposite the findings in the ear normal or pathological

Table II groups together the different organ *systems opposite the most frequently found* aural pathology Negative (normal) ear findings are included and these show whether the general *malformations extended or failed to extend to* the hearing organ

Table III includes some of the syndromes *most frequently associated with changes in the* ear A number of conditions do not fit into the single organ groups and are tabulated separately under Varia" (Table IV) By juxtaposition of the ear pathology if any to the organ group with general malformations, connection between the two units was made more con spicuous.

Among the units of ear pathology the follow ing were the most frequent Otitis neonatorum (12 cases) otitis media suppurativa in more advanced age groups but here it was not possible to be certain whether the start should be placed in the immediate postnatal period Incipient cholesteatoma (3 cases) was restricted to the immediate vicinity of the tympanic *membrane* ("*central cholesteatom Schwarz*, 1963) polyp formation was seen in several cases. Gaucher cells, characteristic for lipoidoses, were seen twice. Bilateral stapedial arteries were present once, with another case in the incipient stage the vessel, originating from the internal carotid *wound around the bottom of the* tym-panic cavity but failed to reach the stapedial region (Kelemen 1958) Malformed stapes was seen three times, always unilateral and once of the type of the étrier coudé (Ombrédanne, 1954) Malformed cochlea was present once Hydrocephalus was observed seven times with and twice without ear *pathology (Niccoli Vallesi* (1958) reporting on a part of this material) No Mondini defect was seen although its appearance is said to be frequent in cases of widespread, general malformations (Illum 1972) Paget-like islands in the bony structure of the inner ear capsule were present several times (cf Kelemen (1970), observed and described in detail).

Anencephaly the most frequent of the mal-formations of the head was lacking from this material The statement of Adair & Potter *(1949) according to which malformations are* commonly observed more frequently in the skull and its contents that in other parts of the body *was corroborated The only runner up group*, was that showing skeletal abnormalities, possibly because deformities of this group are easily observed and will hardly be overlooked

Single ear deformities although recorded in the tables, have been given only a few remarks here warranted for special reasons it was deemed unnecessary to add to the many detailed descriptions extant *Of these only a few* should be mentioned Marx (1926) Nager & de Reynier (1948) Altmann (1957 and 1965) *Schwarz & Becker (1964) Silcox (1967), War* kany (1971) Jorgensen (1972) Terrahe (1972) Sando (1971) presented a series of congenital anomalies of the middle ear subgrouped accord-ing to the presence of associated anomalies of *the latter however it was not yet possible to* compile a comprehensive list because of the small number of histopathological reports.

It has been mentioned that a considerable percentage of the hearing organs was found to be in adequate developmental stage and without pathology in organisms that show a long list of abnormalities in many organs. To these might be added cases in which in what has been *termed above, the "third stage pathology* had *possibly already originated in the second*, or perinatal period An otitis media may develop in a *very short time, even with polyps, cysts*, organizations, exostoses, soon after birth and without strict connection with the neonatus otitis. The latter was declared by *Aschoff (1897)* to be a foreign body otitis, built around fetal

material Thalhammer (1967) stated that the fetus starts to swallow amniotic material as early as the 16th week. Timing difficulties show up in different periods, and considerable caution should be exerted before placing the origin of any pathological sign at a precise point of the teratological timetable

It seems that consensus puts the start of inflammatory manifestations from the fourth fetal month. At this time the inner ear development is already far advanced Dating of ear pathology far back is a hard task not duly emphasized.

The histological work was done at the laboratories of 1) the 2. Surgical Clinic, University of Budapest, Hungary 2) the Mosher laboratory of the Massachusetts Eye and Ear Infirmary Department of Otolaryngology Harvard University Boston, Mass. 3) The Eccles Temporal Bone Laboratory of the Ear Research Institute School of Medicine, University of Southern California, Los Angeles, California.

Discussion

Congenital deformities have always evoked interest Warkany (1963) mentioned that malformations of the ear were already engraved in the tablets of ancient Babylonic scribes, maybe 4 000 years ago The period between 100 A.D. and 1500 A.D has been termed by House (1962) the "dark age of otology" Cook (1838) complained that "from the earliest ages to the present time" pathology of the ear has been almost wholly neglected. But when the early textbooks of otology were prepared, abnormalities were given due attention Pilcher (1838) in his "Essay" offered 22 pages to development and malformations of the ear as introduction to the treatment of the diseases of the latter However he explained that knowledge of these malformations was capable of application in the praxis only to a "slight extent" On the other hand, he found it easy to trace in these malformations a correspondence to permanent structures "of inferior classes" meaning lower animals. Politzer himself (1926), almost a century later declared operative interference in cases of atresia of the external meatus to be useless and further more irrational and dangerous. Since his time rehabilitation of deformities has advanced most decisively as has the knowledge of malformations and their significance in the hearing organs of animals (Kelemen, in press).

Bauer (1945) emphasized that a constitutional biological inferiority of the auditory apparatus occurs in certain strains.

The endless amount of work around the topic has been characterized by Apgar (1963), who said that while in the past few years, attention and interest has been focused on birth defects as never before, otolaryngology has taken its appropriate part in clarification. She pointed to the desirability to put aural deformities into the framework of general malformation of the organism. Nager & de Reynier (1948) complained about the lack of reports on changes of the hearing organ in cases of congenital head malformations. While aural malformations as mentioned by Livingstone & Delahunty (1968) may form an integral part of syndromes such as Treacher-Collins or Wardenburg, rare conditions of congenital deformities are lacking in many clinical descriptions even when recorded as an associated anomaly Berberich (1959 1960) complained that in the enormous literature on birth injuries otologic aspects received comparatively little attention. He tried to integrate ear findings with those in a group of patients admitted for a great variety of conditions, besides birth injury as hydrocephalus, congenital syphilis, chorea, encephalitis, various infectious diseases and nutritional disorders.

The difficulty of enrolling abnormal conditions in one or the other of the three main teratological

periods has been mentioned in several sources. Livingstone (1965) considered it very difficult to know the exact age of the fetus or the date when the damage occurred Ormerod (1960) in his studies on the pathological basis of congenital deafness, found it especially hard to evaluate the date of happenings in the second period between organogenesis and birth Warkany (1971) found the borderlines vague between congenital malformations and congenital microscopic or functional disturbances Lénárt found it not easy to enroll the special case into the first (embryonic) as against the second (fetal) teratogenetic period Bramley (1963) declared it difficult to enroll a progressive hearing loss appearing at any time, at any period Kanizsai (1961) thought that as defects can be attributed to internal or external causes, they can be enrolled into any period of organic development. Benirschke (1967) called attention to the possible interaction of viruses with the fetus as a cause of latent disease multiplicity and ubiquity would find explanation along this line. Luchsinger (1970) stressed the necessity of placing inner ear disturbances as participants in multiple malformations Arnold (1970) emphasized the importance of being aware that congenital and acquired malformations may cause hereditary congenital connatal, or early acquired types of functional disorders.

It may help to accept the chronological classification of Goodhill (1971) which recognizes only hereditary and acquired lesions.

As to the frequency of aural participation in general multiple deformities—*which is our* special interest in this presentation—few data can be found these however are not grouped in a systematic way and differ widely among themselves In his embryological collection comprising 500 pairs of ears, Bollobás (1972) found 18 pairs with developmental anomalies. Crifó & Benincori (1972) estimated that one third of the *general malformations extends to the realm of* the otolaryngologist—a proportion borne out by the here reported series. Fishbein (1963) stated that practically every baby had some minor defect of one kind or another but that most of these already had been outgrown or overcome by the time the child was one year old In other communications single parts of the hearing organ were interpreted *relative* to other parts of this organ as mentioned above deformities can be restricted to single parts of the ear Takahashi & Tsutsumi (1958), in a very detailed analysis, presented microtia against a number of concomitant intraaural conditions. Livingstone (1965) emphasized that, although the outer and middle are deformed, the inner ear may remain *unaffected Comparative pathology too offers many examples of this nature*

Summary

The aim of this presentation was to tabulate participation of the organ of hearing in multiple malformations of the entire organism 54 cases were analyzed with clinical history autopsy protocol and sectional series of the temporal bones extant About one-third showed no ear pathology with some added where abnormalities were restricted to parts of the ear other parts remaining *intact In the* text separate description of single forms of pathology was limited to a few findings, as enumeration of similar signs can be *found* (1) in the tables and (2) in numerous competent publications

Lack of participation of the ear in general deformities in a *comparatively high percentage* was unexpected and did not corroborate the—scarce—data of previous publications, from which, however temporal bone histopathology was mostly absent available here in all cases

Difficulty to assign the origin of a particular defect to a precise point of the teratological timetable, in many cases, was *accentuated*

Zusammenfassung

Die Beteiligung des Gehörorgans an multiplen Missbildungen des Gesamtorganismus wurde dargestellt. 54 Fälle mit klinischer Geschichte, Autopsieprotokoll und Schnittserien der Felsenbeine standen zur Verfügung. Ungefähr ein Drittel der letzteren *zeigte nichts Krankhaftes*, einschliesslich einigen, wo Abnormales auf einen Teil des Ohres beschränkt war. Die Beschreibung von einzelnen Formen der Pathologie wurde begrenzt, da detaillierte Informationen in den Beilagen und in zahlreichen kompetenten Mitteilungen vorliegen.

Die in einem verhältnismässig hohen Prozentsatz minimale Beteiligung des Ohres an allgemeinen Missbildungen war unerwartet und steht im Gegensatz zu Daten früherer Mitteilungen, in denen jedoch keine Felsenbeinpathologie zur Verfügung stand.

Auf die Schwierigkeit, einzelne Defekte einem präzisen Punkt der teratologischen Chronologie zuzuschreiben, wurde hingewiesen.

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Table I

		Autopsy	Aural findings
1 M	13½ w (gest.)	Incomplete fissuring of L lung; bilateral agenesis of kidneys & ureters, oligohydramnios; maternal diabetes mellitus	Normal
2 ?	17 w (abortion)	Cystic hygroma of neck, lymphangiectasis of lung; cerebellar anomalies, polycystic kidney	Hemorrhages in endolymph of semicircular canals, around cristae, tip of cochlea
3. M	19 w (interruption)	Maternal heart disease	Normal
4. M	20 w (interruption)	Maternal nephrosis	Adequate developmental stage
5 F	34 w (premature)	Meningo-encephalocele, occipital microcephaly; microgyria, hypoplasia brain stem, agenesis olfactory bulbs & optic nerves, bilat. microophthalmia, multifocal cerebral calcifications; harelip, cleft palate, persistent ostium primum, persistent L duct of Cuvier; stenosis of aortic ring, cleft mitral valve, left ventricular hypertrophy; accessory spleens, sclerosis & bile duct proliferation periportal regions, liver; polycystic kidneys, uterus didelphys, clubfoot, club hand bilat., bilat. talipes equinovarus; widely separated sutures, recent hemorrhage lat. ventricle	Bilat. persistent, stapedial artery
6. ?	Stillborn	Polycystic kidney	Normal
7 F	Stillborn	Spina bifida, hydrocephalus	R. severe malformation of cochlea, only 1½ turns; no Reissner's; tectorial agglutinated, Corti flat, stria normal, malformed stapes; L Rosenthal canal mostly empty
8 M	Stillborn	Polycystic kidney, penile agenesis, absence of scrotum, cleft palate, harelip; webbing of neck; absence of tongue; polydactylism, situs inversus, cirrhosis of liver; hypoplasia of lungs; accessory spleen; hypoplasia of stomach, undescended testes, hydrocephalus, agenesis of corpus callosum; obliteration of aqueduct, club feet	L.s. exostosis inner ac. meatus, high in vestibular nerve; exostosis of posterior wall of niche of round window
9 M	Stillborn	Hydrocephalus, necrosis of liver & kidney; ? toxoplasmosis	Normal
10 M	1 h	Cerebral congestion, edema, cephalopelvic disproportion, cephalohematoma, hydronephrosis, hydroureter; parathyroid hyperplasia or adenoma, premature involution of adrenal fetal cortex, maternal pseudohypoparathyroidism	Organizing cushions in both windows; obturator foramen; central space in mesenchyme remainder of stapedial artery; calcification in vascular stria, basal turn
11 F	1 h 35 min	Premature, 25 cm CR, polycystic kidney; hypoplasia of lung; encephalocele, occipital hydrocephalus, peculiar liver & adrenals; club feet; bicornuate uterus, wide fontanelles	Carotis, partial course of stapedial artery; excavation of cochlear capsule by carotid canal

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8. M	Stillborn	Polycystic kidney penile agenesis, absence of scrotum cleft palate, harelip webbing of neck, absence of tongue polydactylism, situs inversus cirrhosis of liver hypoplasia of lungs accessory spleen, hypoplasia of stomach, undescended testes hydrocephalus; agenesis of corpus callosum obliteration of aqueduct; club feet	L.s. exostosis inner ac. meatus, high in vestibular nerve; exostosis of posterior wall of niche of round window
9. M	Stillborn	Hydrocephalus, necrosis of liver & kidney ? toxoplasmosis	Normal
10. M	1 h	Cerebral congestion, edema, cephalopelvic disproportion cephalohematoma, hydronephrosis, hydroureter parathyroid hyperplasia or adenoma premature involution of adrenal fetal cortex, maternal pseudohypoparathyroidism	Organizing cushions in both windows obturator foramen. central space in mesenchyme remainding of stapedial artery calcification in vascular stria, basal turn
11. F	1 h 39 min	Premature, 25 cm CR, polycystic kidney hypoplasia of lung; encephalocele, occipital hydrocephalus, peculiar liver & adrenals, club feet; bicornuate uterus, wide fontanelles	Carotis; partial course of stapedial artery excavation of cochlear capsule by carotid canal

		Autopsy	Aural findings
12. M	5 h	Hydrocephalus obstruction of aqueduct intussusception ileum	Int. sulcus, transudate one side
13 F	7 h	Cebocephaly microcephaly (arhinencephaly Kundrat) single imperforate central nostril palatoschisis, central cranial approximation of sutures prematurity 2 100 gr 28 cm CR	Hemorrhages inner meatus & subarach. fossa
14 F	15 h	Extreme prematurity- immaturity severe degree pus in GI tract (? from infected amniotic sac)	Early reabsorption of mesenchyme (more particular considering extreme prematurity)
15 F	44 h	Maternal polio Interventricular & subarachnoidal hemorrhage massive partial involution of thymus, hypoplasia of all organs immaturity of kidneys, intestines, brain lung	Normal
16. F	? d.	Microcephaly cong. heart disease cyanotic type dextrocardia coarctation of aorta septal defect choanal atresia hemangioma of nose umbilical hernia	Round window hyaline mass
17 M	3 d	Cong. heart disease r ventricular hypertrophy & dilatation l. ventricular hypertrophy- hypoproteinemia central nervous system anomalies bilateral corneal opacities, pitting edema of extremities	Lacy bone, reminiscent of Paget s disease, in inner ear
18 M	3 d.	Encephalocele hypoplasia of cerebellum anomalous midbrain shallow post. fossa upward deviation of nerve roots cong. dislocation of hips, bilat. talipes equinovarus fracture of skull large defect, occipital bone (difficult delivery face presentation) large encephalocele	Neonatus otitis media & interna, serofibrinous & suppurative, engorgement, extravasates
19 F	3 d.	Cong. heart disease, interventricular septaldefect overriding aorta, bicuspid, pulmonary valve hypoplasia of lungs Meckel diverticulum accessory spleen hematoma of thyroid prolapse of vaginal mucosa with Gortner duct remnant anomalous growth of cerebellar region multiple hemorrhages in brain cortex, thalamus, cerebellum immaturity of viscera	Hypoplasia of right external ear otherwise normal ear
?0. F	3½ d	Mongolism hydrothorax, bilat club feet fenestration of cups of aortic valve mural thrombus in cardiac ventricle	R. normal left serous labyrinthitis blood in cochlea
21 M	4 d.	Tracheo-esophageal fistula (type C Gross) patent ductus arteriosus agenesis l kidney & ureter single umbilical artery multiple anomalies of vertebral column, incl. hemivertebrae anomalies of circle of W ll s mongolism (paternal ricketts)	Cochlear aqueduct dilatation remnant of stap artery (straightened out) carotid canal deep indentation into cochlear capsule malleus inserted in cyst in tympanic membrane, source of non-inflammatory cholesteatoma
22. M	7 d	Prematurity (37 5 cm, 3 lbs) clouding of cornea cleft palate abnormal position of vocal cords esophageal atresia absence of lung fissure hypoplasia of lungs right aortic arch tetralogy of Fallot hypoplasia of pulmonary artery	Malformation of pinna absence of ext. meatus r malform. stapes (single crus, bulky) ext. canal closed by bony plate,

		Autopsy	Aural findings
		bicuspid stenotic valve; membranous interventricular septal defect; overriding of aorta, malrotation of intestines; annular pancreas; stenosis of duodenum, absence of celiac artery; stenosis of rectum, dilatation of descending colon & sigmoid, hypoplasia of kidneys, cryptorchidism; clubbing of hands; absence of thumbs; absence of radii; hydrocephalus, internal	opens into fibrous mass, L stapes fracture; malleus long process did not develop
23. F	9 d	Renal hypoplasia; micrognathia, bicornuate uterus; skeletal anomalies	R. partial ectasia of tympanic scala, middle turn
24. F	13 d.	Central nervous system: absence of corpus callosum, hypoplasia of cerebellum, hypoplasia of temporal and parietal lobes; bilat. coloboma; ant. displacement of anus, bilobed r. lung; double arterial supply of kidney; hyperextensibility of joints; absence of elastic tissue of skin; cardiomegaly; hepatomegaly; nephromegaly	Normal
25. M	19 d	Hydrocephalus; hypoplasia of olfactory organ, of optic nerve, of fifth nerve; absence of septum pellucidum & corpus callosum; hypoplasia of cerebellum, erosion of ant. clinoid process, malformation of cerebral fossae; hydronephrosis, pulmonary atelectasis	Erosion of petrous bone; neonatus otitis media, probably intrauterine origin, dilatation of all perilymphatic spaces, incl. cochlear aqueduct; some extravasation middle & int. ear (forceps?)
26. F	21 d.	Omphalocele; cong. heart disease, cyanotic; fenestrated valve foramen ovale patent ductus arteriosus; dilated r. atrium, dilated L ventricle; common mesentery for small & large intestines; spina bifida occulta, sacrum, esophageal hiatal defect	Neonatus otitis purulenta, left, rosary row of cysts in mucous membrane
27. F	24 d.	Pulmonary artery coming off r. pulmonary artery and crossing the midline to the left between trachea and esophagus, cardiomegaly; obstructive pleuritis, bilat., diaphragmatic muscle strands attached to lat. chest wall; fusion of right ribs, hemivertebrae on level of 5th & 7th cervical vertebral bodies, dorsal scoliosis	R. hypoplastic external ear; auditory canal not patent, otherwise normal (in spite of breech)
28. M	25 d.	Congenital toxoplasmosis; calcification of cerebral cortex; internal hydrocephalus, hepatomegaly; splenomegaly; interstitial pneumonia, pulmonary edema, solitary cyst of liver; hilar lymphadenopathy; extensive dilatation of ventricular system	Neonatus otitis media, organizing bands
29. F	30 d	Micrognathia; microphthalmia, macrocephaly; bulk nose; narrow arched palate; short neck, flattened cervical vertebrae; low hair line posteriorly; dislocation L hip; L talipes calcaneovarus, overweight brain; tentorial hematoma, inequality r. & L sides of post. fossa; anomalous circle of Willis, cong. heart disease: patent for ovale, ventricular septal defect; biventricular hypertrophy; endocardial sclerosis, coarctation of aorta; patent ductus arteriosus; dilated pulmonary arteries; Meckel diverticulum, accessory diverticulum, non-attachment of mesentery; bands from duodenum to liver & from ileum to cecum, ovarian cyst, simple diaphragmatic hernia; congested liver	R. Paget's-like bone in inner ear capsule, otherwise normal

		Autopsy	Aural findings
30 M	32 d.	Imperforate anus pulmonary hyaline disease cyanotic heart disease microcephaly lacunar skull, 3 fontanelles mongolism intestinal malrotation congenital heart hypoplasia l. atrium, l ventricle, aorta endocardial sclerosis, l atrium premature closure of foramen ovale patent ductus arteriosus r ventricular hypertrophy hypoplasia, left kidney	Normal
31 M	39 d.	Pierre-Robin prematurity cong. heart disease ventricular septal defect hypertrophic r ventricle small mandible recessing of chin high arched palate bicuspid pulmonary valve bicuspid aortic valve widely open ductus arteriosus defect of diaphragm malformation of spleen horseshoe kidneys with multiple renal arteries r inguinal hernia single umbilical artery	Low set ear malformed pinnae otherwise ear normal
32. F	6 w	Hysterotomy bulbar polio	Normal
33 F	4 mo.	Hydranencephaly adrenal atrophy hepatosplenomegaly thymic involution cardiomegaly accessory spleen signs of old meningitis cerebral hemispheres almost completely replaced by membranous sacs filled with serous spinal fluid & some rudimentary cortical tissue	Neonatus otitis, bilat. (sero-fibrinous) sign of central irritation cuffing of vessels in thick polypous tympanic membrane (basal hydrocephalus?)
34 M	7 w	Communicating hydrocephalus subarachnoid-ureteral shunt cerebral edema	Neonatus (intrauterine?) otitis media signs of organization cholesteatoma-sac formation, upper half of tympanic membrane left side
35 M	7 w	Microcephaly cong. lues ? toxoplasmosis hydranencephaly with microcephalus, cong. defect in occipital bone hepatomegaly generalized icterus renal disease with bile necrosis? adrenal hypoplasia undescended r testicle partially differentiated eye	L.s. transudate in several locations, middle ear some organization
36. ?	?	Microtia	Normal
37 F	7½ w	Multiple anomalies hepatitis, neonatal	Reissner pressed to the organ of Corti, r side in the vestibule, perilymphatic edema
38 M	3 mo	Infantile muscular atrophy (Werdnig-Hoffmann) involvement of trunk and limb muscles secondary to anterior horn degeneration in spinal cord without apparent tract disease	Normal
39 M	3½ mo	Treacher-Collins syndrome coloboma palpebrae hypertelorism micrognathia glossoptosis hypoplasia of maxilla & zygomatic arch cleft palate, posteriorly obstruction l nasal passage left choanal atresia fenestration of falx cerebri & tentorium cerebelli pectus excavatum atelectasis of lungs, bilat. atrophy of thymus hemorrhages, focal, submucosal, ileum and colon	Hypoplasia of pinna absence of ext. aud. meatus agenesis of ossicles r stapes single crus from center of foot plate large dehiscence of facial canal incudostapedial articulation absent

		Autopsy	Aural findings
40. M	4 mo.	Clenched fist, flexed great toes deformed chest; fibrous defect of clavicle; short sternum diastasis recti, pancreatic ectopia Meckel diverticulum underdeveloped olfactory bulb & cribriform plate; partial defect of diaphragm incomplete rotation of kidney double renal arteries urachal cyst, partial failure of mesentery accessory pulmonary fissure hypoplasia of iliac arteries delayed & irregular development of skeletal muscles cong. heart disease ventricular septal defect hypoplasia of mitral valve ring venous hypertrophy coarctation patent ductus arteriosus, small patent foramen ovale high arched palate high thymus, persistent l. sup. vena cava bilat. azygos venous system	Malformed middle ear (gross) serous labyrinthitis chronic otitis media extravasates, inner ear l.s. lymphatic edema around utricle malformed stapes *single crus, fused center* of footplate
41 F	3 w	Prematurity 23 weeks gestation intrauterine *fetal death due to placental degeneration* hemorrhages in many organs breech, maternal death 6 hours after delivery Asiatic influenza pharynx washings, large amount of Asiatic flu *strain*	Intrauterine otitis media, serous-sanguinolent deep pockets around malleus formed by desquamated lamellae, potential source of cholesteatoma (sanguinous character common in influenza otitis)
42 F	11 mo.	Marfan syndrome small cranium, coronary synostosis, loose skin poor muscular development bilat. talipes equinovarus, wrist drop bilat dislocation of hips, arthrogryposis, high arched palate; arachnodactyly lenticular denature delayed dentition osteochondrodystrophy Marfan heart & pulmonary disease underweight brain, undernourishment fatty liver hypoplasia of pancreatic islets	R.s. saccus endolymphaticus dilation with edematous papillae, otherwise normal ear
43 F	*16 mo*	Ventricular taps & shunts, 5th revisions noncommunicating hydrocephalus, cyst of 4 ventricle absent inf. vermis, (Dandy-Walker) platybasia, pituitary cyst; absent l. kidney cortical scarring of kidney secondary to healed pyelonephritis, cachexia, anemia, dehydration, multiple gastric ulcerations, minimal gastric hemorrhage, patent ductus arteriosus, cardiomegaly pulmonary artery hypertrophy r. ventricular hypertrophy atelectasis posterior segment of l. lobe absence of mesenteric attachment	Normal
44 F	1 y	Cerebral dysgenesis, atrophy with microcephaly neonatal myoclonus; underdevelopment	Normal gazed in direction of rotation *about* nystagmus
45 F	1 y	Cerebral dysgenesis, atrophy microcephaly underdevelopment	Side? Rosenthal canal empty at base
46 F	2 y	Nephritis, multiple anomalies	Normal
47 F	2 y	Microcephaly severe cerebral & cerebellar atrophy (? rubella)	L.s. severe supp. otitis media, abscess between layers of tympanic membrane

		Autopsy	Aural findings
48. M	½ y	Cong. heart disease, cyanotic, tetralogy of Fallot hypoplastic pulmonary arteries bicuspid pulmonary valve valvular stenosis, pulmonary dextroposition of aorta hypertrophy of r ventricle ventricular septal defect pulmonary stenosis or atresia	L.s. chron. otitis media, advanced organization, beginning of cholesteatom formation large extravasates in lumen of middle ear mucous membrane high polypous, with dense *cellular infiltration, many* resorption buds, windows obliterated, stapes to complete immobilization, large polyp from tubal corner extravasates in carotid canal inner ear intact, end organs in excellent preservation (deafness at admission at 25 mos. ? rubella)
49 M	3 y	Hurler s syndrome (gargoylism)· involvement of brain mitral valve, arteries (aorta, coronaries, sup mesenteric, renal iliac) bladder eyes *(proptosis) subarachnoid cyst overlying* pituitary fossa skeletal changes affecting spinal column & skull short teeth, dysodontia splenomegaly (hyperplasia of white pulp), *hypertrophy of lymph nodes, generalized ridge* around neck of urinary bladder· pulmonary atelectasis, congestion & edema, umbilical hernia mild hirsutism clubbing of fingers, *external hemorrhoids*	R.s. otitis media, massive organization, blocking of windows, abnormal ossification *focus of Gaucher* cells in cochlear capsule, in tegmen large cartilaginous island, with small bone particles *with lamellary* structure, without osteoblasts inf wall of tympanic cavity cartilaginous *space enclosing* exostosis on slender pedicle with central marrow space and cartilaginous cap at distal extremity cochlear capsule lower turn large resorption focus penetrating all layers except endosteal containing, on a fibrous basis, large cells with peripherally spaced nuclei (? Gaucher) no words ever used
50. M	3 y 7 mo.	Ac. poliomyelitis, ac. toxic reaction of lymphoid tissue marked involvement of midbrain, basal ganglia, pons, med oblongata high cervical cord involvement lesser degree of cerebral cortex, cerebellum, lower spinal cord	Normal
51 M	4 y	Hurler s syndrome hepatomegaly hydrocephalus, coronary artery involvement	R.s. chron. otitis media persistence of mesenchymal filling of middle ear blocking both windows *signs of abnormal ossification* fibrous island in mastoid two small osteomas in round window niche calcification in stria vascularis near round window
52. M	7 y 10 mo.	Riley-Day syndrome scaly dry skin of chest alopecia temporal region	Both sides, vestibular aqueduct & saccus *dilatation*

		Autopsy	Aural findings
3 F	8 y 3 mo.	Ac. leukemia with hemorrh. diathesis, gastrointestinal hemorrhage; hepatosplenomegaly: renomegaly with frank hemorrhage into calyces, slight l. ventricular hypertrophy with focal endocardial hemorrhage; generalized petechiae and ecchymoses on epithelial surfaces	R.s. extravasates in endo- and perilymph spaces in vestibule; systolic bruit over mastoid at age 8 years complaints of "hearing things" diplopia, spots in front of right eye
4. M	13 y	Cong. heart disease: atrioseptal defect, cardiomegaly. L ventricular hypertrophy & dilatation, l. pulmonary edema & congestion, hemothorax, hepatic cirrhosis; splenomegaly: renal ischemia, bilat. hypoplastic testes, hypoplastic penis: hypospadias, lipoid depletion of adrenals, mental retardation	Cyst forming med. wall of int. ac. meatus

Table II

	Aural pathology
Circulation	
Cardiomegaly	B.s. neonatus otitis
Cardiomegaly atrial septal defect	0
Cardiomegaly patent duct. arteriosus, r ventricular & pulm. art. hypertrophy	
Cardiomegaly r ventr hypertrophy & dilat.	0
Cardiomegaly patent duct arteriosus, r ventr & pulmonary artery hypertrophy	Cyst in internal meatus
Patent ductus arteriosus	Cochlear duct dilatation incip. cholesth. in tympanic membrane
Patent ductus arteriosus, fenestrated for ovale, dilat. r atrium, l ventricle	Otitis media purul. ? neonat. (21 days)
Patent ductus arteriosus, coarctation of aorta, ventral septal defect, patent for ovale, hypoplasia of mitral valve ring	R.s. serous labyrinthitis, l.s. malformed stapes
Patent ductus arteriosus, coarctation of aorta, patent for ovale, ventricular septal defect, endocardial sclerosis	Paget-like islands in inner ear
Ventricular septal defect, hypertrophy r ventricle	0
R. ventr hypertr & dilatation, l. ventr hypertrophy focal endocard., hemorrhages	Paget-like islands in inner ear extravasates in endo- & perilymph spaces
Fenestration of cups of aortic valve, mural thrombus in cardiac ventricle	L.s. serous labyrinthitis
Interventricular septal defect, overriding aorta	0
Persistent ostium primum, persistent l. duct. of Cuvier stenosis of aortic ring, cleft mitral valve, l ventricular hypertrophy	Bilat. persistent stapedial artery
Dextrocardia, coarctation of aorta, septal defect	Hyalin mass in round window
Involvement of mitral valve, coronaries	R.s. otitis media (3 years)
Cyanotic heart disease	0
Marfan heart & pulmonary disease	Saccus endolymph. dilatation
Hurler coronary artery involvement	Chronic otitis media (4 years) b.s. ca. 60 db hearing loss, middle range
Fallot tetralogy	Malformed stapes & malleus
Fallot tetralogy (rubella)	L.s. chron. polypous otitis media
Maternal heart disease	0
CNS	
Cerebral dysgenesis and atrophy microcephaly	Rosenthal canal empty
Microcephaly cong. defect of occipital lobe	Transudates, organizations
Microcephaly	Otitis med. supp.
Microcephaly 3 fontanelles, mongolism	0
Microcephaly overweight brain, tectorial hematoma, inequity r & l. post. fossa, anomalous circle of Willis	Low-set auricle, Paget-like islands in inner ear capsule
Microcephaly microgyria, hypoplasia of brain stem, shallow post. fossa, agenesis of olfactory bulb & optic nerves, microophthalmia, multifocal cerebral calcifications	Bilateral persistent stapedial artery
Microcephaly cebocephaly arhinencephaly Kundrat, cranial approximation of sutures	Hemorrhages int. meatus & subarcuate fossa
Absence of corpus callosum, hypoplasia of cerebellum, hypoplasia temporal & parietal bones	0
Microgyria	Ectasia tymp. scala, middle turn
Underweight brain, coronary synostosis	Saccus endolymph. dilatation
Occipital encephalocele	Otitis media & int. suppuration
Occipital encephalocele, hypoplasia of cerebellum, anomalous midbrain, shallow post. fossa, upward deviation of nerve roots	
Cerebral edema	Otitis media & int. cholest. sac cyst in tympanic membrane
Cerebral edema, congestion, cephalhematoma	Organization, both windows, calcification in stria
Calcification, cerebral cortex	Otitis media neonat.
Degeneration anterior horn, spinal cord	Catarrhal otitis media
Hypoplasia of olfactory organ, 5th nerve absence of septum pellucidum & corpus callosum, hypoplasia of cerebellum	Otitis media neonat.
"Cerebellar anomalies"	Blood in vestibule & semicirc canals
"Central nervous system anomalies"	Paget-like island in inner ear capsule
Anomalous growth of cerebellum	Hypoplasia, right ear

	Aural pathology
*Involvement of brain	Anomalies of cochlear capsule, otitis media supp.
Platybasia, Dandy-Walker	0
Pierre-Robin	Low set ear, malformed pinnae
Spina bifida	Malformed cochlea
Erosion, ant. clinoid process, of petrous bone, malformation of cerebral fossae	Otitis media neonat.
Mongolism, rickets in father	Cochlear aqueduct dilatation, cyst in tympanic membrane
Mental retardation (13 years)	Cyst, inner acoust. meatus
Poliomyelitis ant., interventricular & subarachnoid hemorrhages	0
Polioencephalitis	0
Maternal bulbar polio	0
Maternal acute polioencephalomyelitis	0
Congenital defect of occipital bones	Catarrhal otitis med., organizations
Signs of old meningitis	Otitis media neonat.
Lungs	
Hypoplasia of lungs	Incipient stapedial artery
Hypoplasia of lungs	Exostosis in int. ac. meatus exostosis in niche of round window
Hypoplasia of lungs, absence of lung fissure	Malformed stapes
Bilobed right lung	0
Atelectasis of lungs	Malformed stapes
Atelectasis of lungs	Ot. med. neonat.
Atelectasis of lungs, congestion, edema (Hurler)	R. otitis media
Pulmon. edema, congestion, hemothorax	*Cyst*, int. acoustic meatus
Hydrothorax, bilat.	Serous labyrinthitis
Pulmonary hyaline disease	*0*
Intestines	
Umbilical hernia	Hyalin mass at round window niche
Diaphragmatic hernia	0
Inguinal hernia	0
R. inguinal artery	0
Immaturity of viscera	Hypoplasia r. ext. ear
Immaturity of viscera	0
Situs inversus, hypoplasia of stomach	Exostosis inner meatus, exostosis niche of round window
Malrotation of intestines, annular pancreas, stenosis of duodenum	Malformed stapes
Intussusception, ileum	Scattered transudates in middle ear
Common mesentery for small & large intestines	Otitis purulenta neonat.
Celiac artery absence	Malformed stapes
Meckel diverticulum, non-attachment of mesentery, bands from duodenum to liver, to ileum, to cecum, diaphragmatic hernia	Paget-like islands in inner ear capsule
Meckel diverticulum, pancreatic ectopia, diastasis recti, partial failure of mesentery, hypoplasia iliac arteries	R. serous labyrinthitis, L malformed stapes
Defect of diaphragm	0
Gastrointestinal hemorrhages	Many extravasates
Multiple gastric ulceration, gastric hemorrhage, absence of mesenteric attachments	0
Hemorrhages, submucous in ileum, colon	Malformed stapes
Pancreatic ectopia	Serous labyrinthitis, malformed stapes
Displacement of anus	0
Single umbilical artery	0
Single umbilical artery	*0*
Spleen	
Splenomegaly (hyperplasia of white pulp)	Otitis med.
Splenomegaly (hyperplasia of white pulp)	Cyst, *inner* acoust. meatus
Hepatosplenomegaly	Otitis media neonat.
Accessory spleen	Exostosis inner meatus, exostosis niche of round window
Accessory spleen	Hypoplasia external ear
Malformation of spleen	0
*Hypoplasia of all organs	*0*

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Patent ductus arteriosus, coarctation of aorta, patent for ovale, ventricular septal defect, endocardial sclerosis	Paget like islands in inner ear
Ventricular septal defect, hypertrophy r ventricle	0
R ventr hypertr & dilatation, l ventr hypertrophy focal endocard. hemorrhages	Paget-like islands in inner ear extravasates in endo- & perilymph spaces
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Interventricular septal defect, overriding aorta	0
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Microcephaly cebocephaly arhinencephaly Kundrat, cranial approximation of sutures	Hemorrhages int. meatus & subarcuate fossa
Absence of corpus callosum, hypoplasia of cerebellum, hypoplasia temporal & parietal bones	0
Microgyria	Ectasia tymp. scala, middle turn
Underweight brain, coronary synostoses	Saccus endolymph. dilatation
Occipital encephalocele	Otitis media & int suppuration
Occipital encephalocele, hypoplasia of cerebellum, anomalous midbrain, shallow post fossa, upward deviation of nerve roots	
Cerebral edema	Otitis media & int. cholest sac cyst *in tympanic membrane*
Cerebral edema, congestion, cephalhematoma	Organization, both windows, calcification in stria
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Pierre-Robin	Low set ear malformed pinnae
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Mongolism, ricketts in father	Cochlear aqueduct dilatation, cyst in tympanic membrane
Mental retardation (13 years)	Cyst, inter. acoust. meatus
Poliomyelitis ant., interventricular & subarachnoid hemorrhages	0
Polioencephalitis	0
Maternal bulbar polio	0
Maternal acute polioencephalomyelitis	0
Congenital defect of occipital bones	Catarrhal otitis med., organizations
Signs of old meningitis	Otitis media neonat.
Lungs	
Hypoplasia of lungs	Incipient stapedial artery
Hypoplasia of lungs	Exostosis in int. ac. meatus exostosis in niche of round window
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Pulmon. edema, congestion, hemothorax	Cyst, int. acoustic meatus
Hydrothorax, bilat	Serous labyrinthitis
Pulmonary hyalin disease	0
Intestines	
Umbilical hernia	Hyalin mass at round window niche
Diaphragmatic hernia	0
Inguinal hernia	0
R. [illegible] artery	0
Immaturity of viscera	Hypoplasia ext. ear
Immaturity of viscera	0
Situs inversus, hypoplasia of stomach	Exostosis inner meatus, exostosis niche of round window
Malrotation of intestines, annular pancreas, stenosis of duodenum	Malformed stapes
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Gastrointestinal hemorrhages	Many extravasates
Multiple gastric ulceration, gastric hemorrhage, absence of mesenteric attachments	0
Hemorrhages, submucosa in ileum, colon	Malformed stapes
Pancreatic ectopia	Serous labyrinthitis, malformed stapes
Displacement of anus	0
Single umbilical artery	0
Single umbilical artery	0
Spleen	
Splenomegaly (hyperplasia of blue pulp)	Otitis med.
Splenomegaly (hyperplasia of blue pulp)	Cyst, inner acoust. meatus
Hepatosplenomegaly	Otitis media neonat.
Accessory spleen	Exostosis inner meatus, exostosis niche of round window
Accessory spleen	Hypoplasia r. external ear
Malformation of spleen"	0
Hypoplasia of all organs	0

	Aural pathology
Liver	
Hepatomegaly	*0*
Hepatomegaly	Chronic otitis med.
Hepatomegaly	Otitis med. neonat.
Hepatosplenomegaly	Catarrhal otitis, organizations
Congested liver	Paget like island inner ear capsule
Hepatitis, neonatal	Vestibule perilymph. edema, Reissner depressed
Necrosis liver & kidney	0
Hepatic cirrhosis (stillborn)	Exostosis inner meatus, exostosis niche of round window
Hepatic cirrhosis (13 years)	Cyst, inner acoust. meatus
Solitary cyst of liver	Otitis med. band formation
Kidney	
Absent l. kidney	*0*
Agenesis l. kidney	Dilated cochlear aqueduct
Bilat. agenesis of kidney & ureter	*0*
Immaturity of kidney	0
Immaturity of kidney	0
Renal hypoplasia	*0*
Renal hypoplasia	Ectasia tymp scalae middle turn
Renal hypoplasia	Otitis med neonatorum
Horseshoe kidney multiple renal arteries	0
Nephromegaly	*0*
Nephromegaly hemorrhage into calyces	Many inner ear hemorrhages
Renal ischemia	Cysts, inner acoust. meatus
Hydronephrosis	Otitis med. neonatorum
Hydronephrosis, hydroureter	Organizations, esp. in windows
Polycystic kidney	*0*
Polycystic kidney	Multiple hemorrhages, med & int. ear
Polycystic kidney	Multiple exostoses
Polycystic kidney	Incipient stapedial artery
Calcification of renal cortex	Otitis media neonatorum
Nephritis	0
"Renal disease"	Catarrhal otitis med., organizations
Maternal nephritis	0
Adrenal cortex abnormalities	Organizations, both windows
Male sex organs	
Ureter agenesis	Origin of non-inflammatory cholesteatoma
Hydroureter	Organization in both windows
Pus in GI tract	*0*
Urachal cysts	Serous labyrinthitis, malformed stapes
Hypospadias	Cyst in int. acoustic meatus
Cryptorchismus	Malformed stapes
Undescended testicle	Transudates, organizations
Female sex organs	
Uterus duplex	Ectasia tympanic scala, medial turn
Uterus duplex	Bilat. stapedial artery
Uterus duplex	Incipient stapedial artery
Ovarian cyst	Paget-like islands in inner ear capsule
Prolapse of vaginal mucosa, with Gartner-duct remnant	0
Oligohydramnios	0
Intrauterine fetal death due to decidua placental degeneration	Intrauterine otitis
(Hysterotomy bulbar polio)	
(Breech presentation)	Intrauterine otitis
(Face presentation)	Neonatus otitis, extravasates
Eye	
Micro-ophthalmia	Bilat. stapedial artery
Proptosis	Unilat. otitis media
Clouding of cornea	Malformed stapes & malleus
Coloboma palpebrae inf	Malformed stapes
Coloboma, bilat.	0
Hypoplasia of optic nerve	Otitis med. neonatorum

	Aural pathology
Skin	
Hirsutism	Otitis media
Scaly dry skin on chest	Very wide vestibular aqueducts, b.s.
Absence elastic tissue of skin	0
Petechiae, ecchymoses on epithelial surfaces	Endo- & perilymph extravasates in vestibule
Hemangioma of nose	Hyalin mass in round window
Pitting edema of extremities	Paget-like islands in capsular bone
Low hairline	Paget-like islands in capsular bone
Single imperforated central nostril	Hemorrhages, inner auditory meatus
Cystic hygroma of neck	Multiple hemorrhages in inner ear
Skeleton (outside skull)	
Skeletal changes, spinal column & skull	Otitis media
Fusion of ribs	0
Hemivertebrae, level of 5 & 7 cerv. vert.	0
Spina bifida	Cochlear malformation b.s.
Spina bifida occulta	Otitis purulenta neonatorum
Dislocation of cerv. vertebrae, micrognathia, beak nose, narrow arched palate, dislocation of l. hip, l. talipes calcaneovarus	Paget-like island in inner ear capsule
Dislocation of hip	Neonat. otitis media & interna, serous & supp.
Small mandible, recession of chin, arched palate, Pierre-Robin	0
Micrognathia, glossoptosis	Stapedial deformity
High arched palate, short sternum, *fibrous defect in clavicle*, clenched fist, flexed great toes	Otitis media, stapedial deformity
Osteochondrodystrophy, dislocation of hips, high arched palate, arachnodactyly, arthrogryposis, wrist drop, Marfan syndrome	Dilated saccus r.s.
Hyperextensibility of joints	0
Cleft palate, choanal atresia, pectus excavatum	Absence of ext. meatus, agenesis of ossicles, stapedial deformity
Cleft palate, absence of thumbs, clubbing of hands, absence of radii	Absence of ext. meatus, malformed pinna
Club foot, club hand, 6 toes on each foot, bilat. talipes equinovarus	Bilat. stapedial artery
Club feet	Incipient stapedial artery
Club feet	Serous-hemorrhageous labyrinthitis
Skeletal anomalies	Partial ectasia of tympanic scala in middle turn
Multiple *congenital* anomalies	Hypoplasia, r. ear
Teeth: dysodontia	Otitis med., Gaucher cells in cochlear capsule
Delayed dentition (11 months)	Saccus with edematous papillae

Table III

Syndromes	Aural pathology
Marfan (arachnodactyly)	Stenosis paret of vestibular aqueduct
Hurler (lipochondrodystrophy)	Organizations, ossifications, persistent mesenchyme
Tay Sachs (amaurotic familial idiocy)	Chronic mucopurulent otitis media
Hoffmann Werdnig (spinal progressive muscular dystrophy)	Slight inflamm. irritation, middle ear
Pierre-Robin (cleft palate, small mandible, glossoptosis)	0
Riley Day (familial dysautonomia)	Cong. hearing loss, dilatation of *vestibular aqueduct*
Autosomal trisomy	Mucopurulent otitis media, serous labyrinthitis
Fallot tetralogy (dextroposition of aorta, hypertrophy of r ventricle, ventricular septal defect, pulmonary stenosis)	Chronic otitis media (2½ years)
Dandy Walker (platybasia, cebocephaly)	Hemorrhages in inner meatus & subarcuate fossa
Treacher-Collins (dysostosis mandibulofacialis)	Malformed stapes
Mallory Weiss (bronchitis, upper GI bleeding)	*Dilatation of vestibular aqueduct b.s.*
Kundrat (K s lymphosarcoma)	Hemorrhage int. meatus & subarcuate fossa
Cuvier s duct (the common cardinal veins)	Bilat. persistent stapedial artery
Pendred (cong. deafness & goiter)	
Mongolism (trisomy 21)	Serous labyrinthitis, blood in cochlea

Table IV

Varia	Aural pathology
Congenital lues	Transudates, organizations
Leukemia, hemorrhagic diathesis	Many extravasates in endo- and perilymph spaces
Hemorrhages, many organs	Intrauterine otitis, serosanguinolent
Hypoproteinemia	Paget like islands
Cachexia, dehydration	0
Trisomy 17–18	*Malformed stapes*
Maternal diabetes mellitus	0
Thymic involution	Neonatus otitis
Hamartoma of thyroid	0
Hypertrophic lymph nodes, generalized	0 (3 years)
Ac. toxic reaction of lymphoid tissue	0
Early stillborn	0
Extreme prematurity	0
Parathyroid hyperplasia (? adenoma)	Organization in both windows
Neonatal myoclonus	0
Toxoplasmosis 1	0
Toxoplasmosis 2	Transudates, organizations
Toxoplasmosis 3	Neonatus otitis
Abnormal position of vocal cords	Malformed stapes

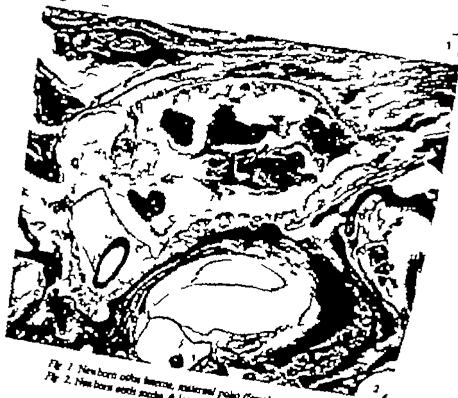


Fig. 1. New born otitis interna, maternal polio (female, 44 hours). ×200

Fig. 2. New born otitis media & interna, [illegible] (female, 7 weeks). ×7

Table III

Syndromes	Aural pathology
Marfan (arachnodactyly)	Stenosis paret. of vestibular aqueduct
Hurler (lipochondrodystrophy)	Organizations, ossifications, persistent mesenchyme
Tay Sachs (amaurotic familial idiocy)	Chronic mucopurulent otitis media
Hoffmann-Werdn g (spinal progressive muscular dystrophy)	Slight inflamm. irritation, middle ear
Pierre-Robin (cleft palate, small mandible, glossoptosis)	0
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Autosomal trisomy	Mucopurulent otitis media, serous labyrinthitis
Fallot tetralogy (dextroposition of aorta hypertrophy of r ventricle, ventricular septal defect, pulmonary stenosis)	Chronic otitis media (?1 years)
Dandy Walker (platybasia, cebocephaly)	Hemorrhages in inner meatus & subarcuate fossa
Treacher-Collins (dysostosis mandibulofacialis)	Malformed stapes
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Kundrat (K s lymphosarcoma)	Hemorrhage int. meatus & subarcuate fossa
Cuvier s duct (the ⊥ common cardinal veins)	Bilat. persistent stapedial artery
Pendred (cong. deafness & goiter)	
Mongolism (trisomy 1)	Serous labyrinthitis, blood in cochlea

Table IV

Varia	Aural pathology
Congenital lues	Transudates, organizations
Leukemia, hemorrhagic diathesis	Many extravasates in endo- and perilymph spaces
Hemorrhages, many organs	Intrauterine otitis, serosanguinolent
Hypoproteinemia	Paget like islands
Cachexia dehydration	0
Trisomy 17 18	Malformed stapes
Maternal diabetes mellitus	0
Thymic involution	Neonatus otitis
Hamartoma of thyroid	0
Hypertrophic lymph nodes, generalized	0 (32 years)
Ac. toxic reaction of lymphoid tissue	0
Early stillborn	0
Extreme prematurity	0
Parathyroid hyperplasia (? adenoma)	Organization in both windows
Neonatal myoclonus	0
Toxoplasmosis 1	0
Toxoplasmosis 2	Transudates, organizations
Toxoplasmosis 3	Neonatus otitis
Abnormal position of vocal cords	Malformed stapes

Fig. 4. Newborn otitis, granulation stage, in reabsorption. Microcephaly (male, 7 weeks). 100.
Fig. 5. Newborn serous labyrinthitis. Maternal polio (female, 44 hours). 400, phase.

3a

3b

Fig. 3a. Newborn otitis, hemorrhageous. Maternal influenza (female, 4 months). 35.
Fig. 3b. Newborn otitis, hemorrhageous. Maternal influenza (female, 4 months). 30.

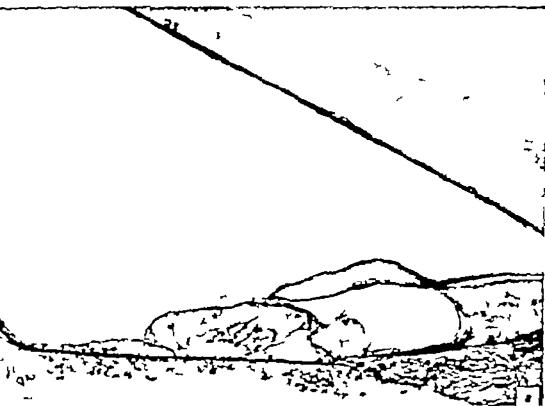


Fig. 8. Congenital hydrocephalus (female, 10 days). 250



Fig 6 Cochlear hemorrhages birth injury ? forceps (newborn)
Fig 7 Congenital hydrocephalus (male, 2 months). 14.5

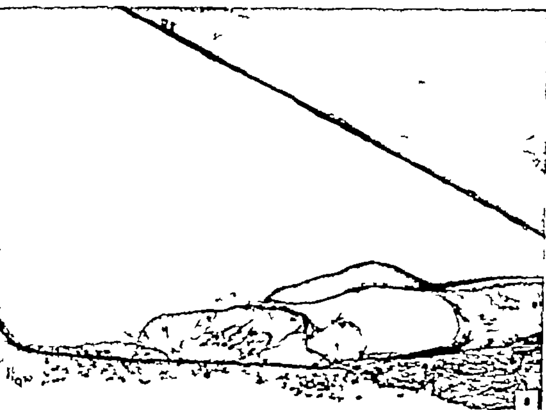


Fig. 8 Congenital hydrocephalus (female, 10 days) 250





Fig 9a. Hemorrhageous otitis media. Fallot tetralogy (male, [illegible] years) × 75.
Fig 9b. Hemorrhageous otitis media. Fallot tetralogy (male [illegible] years). × 50.



Fig. 10 Brain reabsorption. Congenital toxoplasmosis (male, 11 days).
Fig. 11 Organizing otitis media in reabsorption. Congenital toxoplasmosis (male, 11 days). 10.



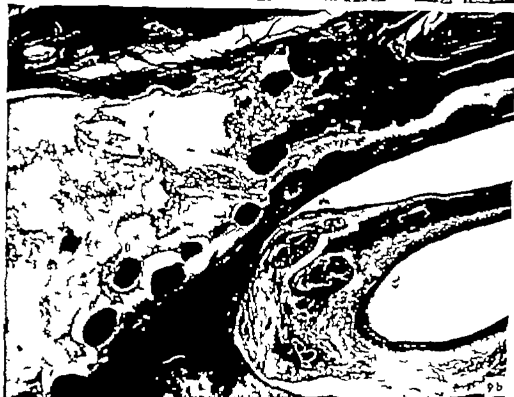


Fig 9a. Hemorrhageous otitis media. *Fallot* tetralogy (male, 2½ years). 7.3

Fig 9b. Hemorrhageous otitis media. Fallot tetralogy (male 2½ years). 250.





Fig 14 Atresia of external auditory canal (female, 10 years)
Fig 15. Osseous canal through pyramid, through arch of superior semicircular canal, congenital.

12

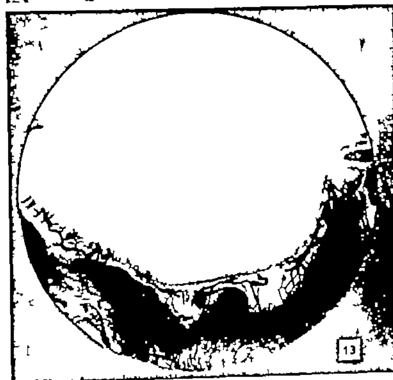


Fig 12 Mesenchyme capillary engorgement with cuffing. Congenital toxoplasmosis (male, 11 days). 250

Fig 13 Injection of tympanic mucous membrane. Congenital syphilis, (few hours post partum)





Fig 14 Atresia of external auditory canal (female, 10 years).
Fig 15 Osseous canal through pyramid, through arch of superior semicircular canal, congenital.



Fig 16 Cystic enlargement of a pneumatic cell at entrance of internal acoustic meatus (male, 13 years). 10.
Fig 17 Exostosis in (closed) external acoustic meatus (female, 10 years).



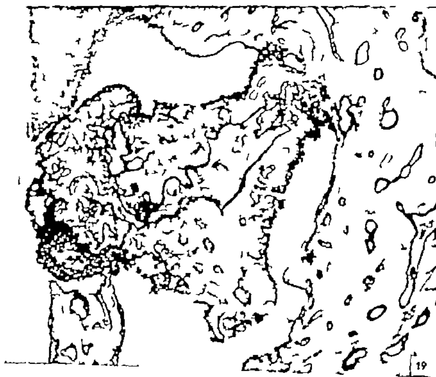


Fig 18 Exostosis in inner acoustic meatus (male, stillborn). 27.5
Fig 19 Exostosis amid fibrous resorption areas of the tympanic wall. Hurler (male, 3 8/12 years). 35

Fig 20 Fibrous resorption focus f cochlear capsule. Hurler (male, 3 8/12 years). 75
Fig 21 Stapes immobilization, congen tal bony fixation of lateral crus. Microcephaly (male, 9 weeks). 20.



23

Fig. 22. Stapes immobilization, congenital arrested opening of the annular articulation (female, 10 years).

Fig. 23. Stapes malformation. Lateral crus lacking, medial crus rising from center of footplate (male, 4 months). 20.

24



Fig 24 Stapes malformation single, massive crus surrounded by extravasates (male, 7 days). × 40.
Fig 25 Stapes malformation arch over medial half of footplate Vestige of stapedial artery (female, 10 years).

Fig 26. Stapedial artery thrombosed (female, premature, 34 weeks) 12 4.

Fig 27 Stapedial artery Trisomy (male, 4 months). 30.

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SUPPLEMENT 318

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ACTA OTO LARYNGOLOGICA

SUPPLEMENT 318

CORRELATIONS OF NASAL SYMPTOMS AND SIGNS IN RANDOM SAMPLING STUDY

BY

JUHANI VAINIO-MATTILA

FROM THE OTOLARYNGOLOGICAL CLINIC
OF CENTRAL HOSPITAL OF KOTKA, FINLAND

KOTKA 1974

CONTENTS

icteristic features of the face, sometimes different from each other can be found g different human races. The nose an important part as this kind of icteristic feature of the face. The shape nose for each race and ethnic group ndamentally different and every mem of any race has a nose which is as nct and different from his neighbor s re his fingerprints.

l (1963) described different prototypes e profile of the face according to Greek, ptian, Renaissance, and modern sculp-s. As stated by Altman (1965) the pro- described by Baud mainly correspond he esthetic ideal of the particular era, to the racial characteristics. According him a prominent bony pyramid and tively small nasal bones are the main erences between the noses of human igs and the other primates.

e to the position and prominence of the e, it is subject to frequent injuries, which y cause a variety of deformities. Traumas y occur during fetal life, during delivery at any time after that. The factors of e, genes, and trauma are the three most portant factors which determine the ulti ate architecture of the nose.

cording to Williams (1956) all human es have very similar functions but the e of a white man is especially efficient an air warming device while the nose of a negro is more effective as air-cooling apparatus than the white man s.

Very little attention has been paid to the relationship between a cosmesis and function. Only recently (Ogura *et al* 1964 Cottle, 1968 Ogura, 1970 Drettner 1970) has the significance of the functions of the nose to the functions of all other organs in the body become obvious. It has not, however been possible to find out what kind of a nose would be the most practical aid to the total organism considering racial differences, variations in climate, physical capacities required, and esthetic factors. As stated by Hinderer (1971) the interrelationship be tween nasal function and other functions of the body necessitates a thorough under standing of the complex structure of the nose and of its reaction to trauma, inflam mation and surgery

To solve the most complicated rhinologic problems concerning nasal structure and functions it seems apparent that modern computer analysis is necessary because the possible relationships to local and distant symptoms, racial, ethnic, and environmental factors, numerous notes from the clinical record like trauma, weight at birth, heredity state of health etc. have to be taken into consideration in correlation studies. It is also necessary to use rhinomanometric, ex aminations of nasal respiration to get figures, which can be handled by a computer

REVIEW OF LITERATURE

Anthropological Aspects of the Nose

General anthropological aspects

The shape of the nose has been one of the items of the anthropological studies which started towards the end of the eighteenth century (Slotkin, 1965). At the present state of the development of this science the length, height, and breadth of the nose and the relationships between these factors have been the objects of measuring. The nose of the white race is described as long and prominent while the negroid nose is broad and flat. In the case of the red and yellow races the measurements of the nose are somewhere between those two (Hinderer 1964). From the measurements of the nose different indices have been calculated for numerical description and anthropological characterization of the nose.

Characterization of the nose with indices and other nasal measurements

Schemes of some nasal indices are described in fig. 1. A detailed method of measuring these indices is presented later (pp. 23—24). *The anthropological nasal index* described by Topinard (1878) can be measured only on the skull. Topinard also described *the cephalometric nasal index* which is measured on living subjects. It can further be subdivided into *a height-breadth index* and *a projection-breadth index*.

The height in living people is measured from nasale to subnasale. The nasale is a point on the skin over the nasofrontal suture in the midline. The subnasale is a point on the skin in the midline immediately below the anterior maxillary spine (anterior nasal spine). The breadth measures the degree of lateral expansion of the anterior nares on the level of nostrils. The antero-posterior projection is measured from the tip to the subnasale.

It has been stated by Williams (1956) that cephalometric nasal index is valuable on the basis of cosmesis so that it cannot be ignored in plastic surgery. Although there are many articles on anthropological nasal indices showing structural and racial differences, there is no indication (Hinderer 1964) that these indices could be applied clinically. *A clinical nasal index* was suggested in 1954 by Cottle (Hinderer 1964) in the evaluation and diagnosis of some rhinological problems.

$$\text{Anthropological nasal index} = \frac{100 \times \text{width of the nose}}{\text{height of the nose}}$$

$$\text{Height-breadth index} = \frac{100 \times \text{maximum breadth}}{\text{maximum height}}$$

$$\text{Projection-breadth index} = \frac{100 \times \text{maximum projection}}{\text{maximum breadth}}$$

Table 1 Division of index values in different race groups

Indices	Hyper leptorr	Leptorr	Mesorr	Chamaerr	Hyper chamaerr
Cephalometric nasal index	<55	55—69.9	70—84.9	85—99.9	≥100
Clinical nasal index		61>	61—65	65—80	
Tip index		60—75	75—80	≥80	
Salience index		55—65			

Cottle assumed that different anatomical types of noses had their own characteristic functional patterns. For instance, when reconstructive surgery of the nose is planned, the anatomical structure and functional pattern characteristic of the race to which the nose belongs must be taken into consideration (Williams, 1956).

A tip index whereby the tip or lobule can be measured has also been presented by Cottle (Hinderer 1964).

There is one *salience index* for each side of the nose. If the dorsum of the nose is prominent, the salience is high. In the white race the projection of the dorsum is 20–30 mm and the projection of the tip 34–42 mm (Cottle, 1960).

Index values in different race groups are seen in table 1. Hyperleptorrhine and leptorrhine = white race, mesorrhine = yellow race, chamaerrhine (platyrrhine) and hyperchamaerrhine = colored race (Williams, 1956, Hinderer 1964).

It is possible to get an even more precise total picture of the nose by using auxiliary examinations like measuring the sizes of separate structural elements and various angles (Joseph, 1967). An ideal nasolabial angle among white men is 85–90, among women slightly higher 95–105. In children it tends to be 100° or higher. The frontonasal angle should ideally be 30–35 (Schultz, 1918). Jenner (1954) has stressed the importance of photography in evaluating the appearance of external nose before and after operations.

Anthropology of the Finnish nose

The earliest ancestors of the present Finns immigrated to this country across the Gulf of Finland during the first thousand years A.D. (Nevanlinna, 1972). The population of the eastern parts of the country (Karelia) has probably also originated as a result of immigration from South Western Finland (Hornborg 1965). The present population of Kotka consists of natives of Kymenlaakso district as well as of Karelian evacuees. The population in Finland is quite young from a genetic point of view and in this respect the inhabitants of Kotka can indeed be considered as representing the population of the whole country. Despite the homogenity of population foreign genetic interference from the east is possible but according to Nevanlinna this can only have happened to a small extent. This opinion has been based on certain examinations of blood groups.

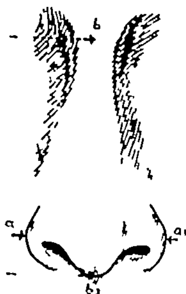
Some studies of the characteristic features of the nose among the inhabitants of different provinces (historical provinces of Finland are presented in figure 2) have been made.

According to Retzius (1878) the inhabitants of Häme province have a small rather broad nose, which often has a small tip bent slightly upwards. The Karelians are said to have harmonious long noses. Karelian women have a straight and rather sharp nose.

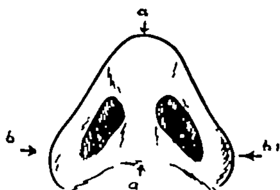
Figure 1



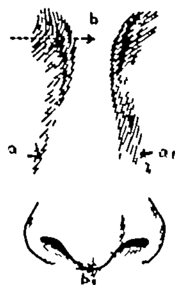
Anthropological Nasal Index



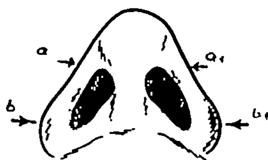
Height Breadth Index



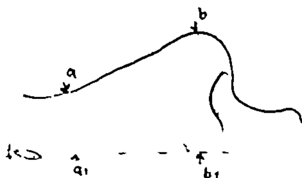
Projection Breadth Index



Clinical Nasal Index



Tip Index



Salience Index

Table . Measurements and Cephalometric Indices of the Finnish Nose

Provinces	sex	number	breadth cm	height cm	projection cm	height-breadth index	projection-breadth index
Etelä-Pohjanmaa	m	298	34.61	58.02	23.25	59.20 ± 0.470	67.41 ± 0.549
	f	471	30.17	53.09	20.18	56.68 ± 0.333	67.10 ± 0.961
Karjala	m	724	33.07	53.57	22.53	63.80 ± 0.330	65.85 ± 0.444
	f	485	31.40	51.58	20.08	61.97 ± 0.376	65.9_ ± 0.569
Savo	m	505	34.73	51.65	23.51	68.42 ± 0.310	67.31 ± 0.506
	f	376	30.99	47.56	21.22	65.79 ± 0.495	68.67 ± 0.624
Uusimaa	m	183	33.22	54.51	1.51	65.29 ± 0.671	61.45 ± 0.741
	f	191	31.94	45.68	19.49	65.57 ± 0.509	61.41 ± 0.605
Satakunta	m	460	35.32	57.65	23.15	62.03 ± 0.423	66.31 ± 0.504
	f	646	31.78	52.57	20.40	61.09 ± 0.379	65.17 ± 0.449
Häme	m	428	33.33	53.72	2_.53	68.59 ± 0.434	64.34 ± 0.500
	f	402	31.85	50.75	21.47	63.21 ± 0.411	68.25 ± 0.555
Turun saaristo	m	147	35.04	57.08	20.51	61.74 ± 0.637	58.56 ± 0.574
	f	103	32.05	52.19	17.79	61.47 ± 0.695	55.73 ± 0.671
Ahvenanmaa	m	182	34.83	54.22	19.76	64.00 ± 0.341	73.16 ± 0.39
	f	257	31.74	50.76	19._1	62.91 ± 0.418	60.55 ± 0.560
Varsinais-Suomi	m	335	35.27	53.50	22.35	64.63 ± 0.461	64.03 ± 0.598
	f	127	33.10	46.56	19.41	72._5 ± 0.958	58.76 ± 08._5

Table 4 Racial Division of the Finnish Nose (per cent)

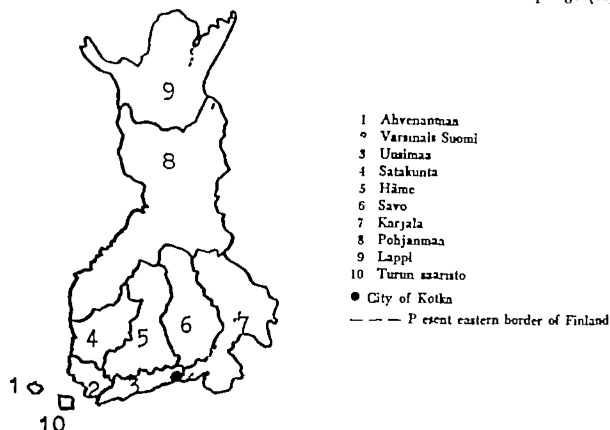
Provinces	sex	hyper leptorr	leptorr	mesorr	chamaerr	hyper chamaerr
Etelä-Pohjanmaa	m	26.9	65.7	7.4	—	—
	f	42.9	53.1	4.0	—	—
Karjala	m	14.0	65.2	19.4	1.1	0.3
	f	22.8	41.7	14.7	0.8	—
Savo	m	9.4	49.5	33.3	6.6	1.2
	f	10.3	59.1	27.6	2.7	0.3
Uusimaa	m	13.1	56.5	29.0	1.1	0.3
	f	4	65.9	31.6	0.5	—
Satakunta	m	22.5	59.8	15.9	1	—
	f	27.9	58.1	11.7	1.9	0.3
Häme	m		60.1	25.6	9.4	0._
	f	14.0	65.1	16.0	0	—
Turun saaristo	m	19.0	66.0	15.6	1.4	—
	f	16.5	73.8	8.7	1.0	—
Ahvenanmaa	m	8	66.0	21.9	—	—
	f	11.3	58	15.5	—	—
Varsinais-Suomi	m	3.4	63.0	29.6	2.0	—
	f	4.3	4—	35.4	14.4	—

In the beginning of this century the methods of measuring the nose were slightly different from modern methods.

In 1925 Kajava gave directions as how to make anthropological examinations. He subdivided the nose into seven parts: root, dorsum, tip, alae, columella, nostrils and nares. The variations of the dorsum of the nose, for instance, were:

narrow, ordinary, broad, very concave, slightly concave, straight, slightly convex, very convex, irregular, humpy, long, medium, short. The septum was not included in his examinations.

Figure 2 Historical provinces of Finland (1 9) and Turku archipelago (10)



The first systematic anthropological examinations of the inhabitants of our country were made by C v Haartman (1845) His references to the nose are, however rather few According to Haartman Karelians have a beautiful straight nose. The inhabitants of the province of Savo have a small nose and the inhabitants of Hame have a small snub nose. It seems to be a common opinion that Finnish nose has a concave profile. This belief is supported by the results of the examinations made by Mustakallio and Telkka (1951) as well as by Arho (1934) presented in table 2

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Table 2 Profile of the Finnish nose (per cent distribution)

Provinces	sex	number	concave	straight	con ex	irregular
Etelä Pohjanmaa	m	998	41.5	38 6	10 6	9..
	f	471	40 4	48 0	8.5	3 1
T run saarist	m	147	29.9	52 1	10.4	7.6
	f	103	48 0	37.3	4 9	9 8
Ahvenanmaa	m	182	17.5	15.9	31.6	35 0
	f	257	51.8	14..	13 0	21 0
Varsinais-Suom	m	335	35 7	32.3	10.3	1 7
	f	127	66.9	15 7	9 5	14.9

Table 3 Measurements and Cephalometric Indices of the Finnish Nose

Provinces	sex	number	breadth cm	height cm	projection cm	height-breadth index	projection-breadth index
Etelä Pohjanmaa	m	598	34.61	58.82	23.23	59.20 ± 0.420	67.41 ± 0.540
	f	471	30.17	53.09	20.16	58.66 ± 0.383	67.10 ± 0.561
Karjala	m	724	35.07	55.57	22.33	63.60 ± 0.350	63.65 ± 0.444
	f	485	31.40	51.38	20.08	61.97 ± 0.376	63.92 ± 0.560
Savo	m	595	34.73	51.65	23.51	68.42 ± 0.510	67.71 ± 0.506
	f	376	30.99	47.58	21.22	65.78 ± 0.498	68.67 ± 0.624
Uusimaa	m	185	35.22	54.51	21.51	65.29 ± 0.671	61.45 ± 0.741
	f	191	31.84	48.68	19.49	65.87 ± 0.509	61.41 ± 0.605
Satakunta	m	460	35.32	57.85	23.13	62.03 ± 0.423	66.21 ± 0.504
	f	646	31.78	52.57	20.40	61.03 ± 0.379	65.17 ± 0.439
Häme	m	426	35.35	53.72	22.53	66.39 ± 0.454	64.34 ± 0.500
	f	402	31.85	50.75	21.47	63.21 ± 0.411	68.28 ± 0.535
Turun saaristo	m	147	33.04	57.08	20.51	61.74 ± 0.637	58.86 ± 0.578
	f	103	32.05	52.19	17.79	61.87 ± 0.693	55.73 ± 0.871
Ahvenanmaa	m	182	34.68	54.22	19.76	64.60 ± 0.541	57.16 ± 0.759
	f	257	31.74	50.76	19.21	62.91 ± 0.418	60.55 ± 0.560
Varsinais-Suomi	m	335	35.27	53.50	22.55	66.63 ± 0.461	64.05 ± 0.595
	f	127	33.10	46.85	19.41	72.25 ± 0.968	58.76 ± 0.825

Table 4 Racial Division of the Finnish Nose (per cent)

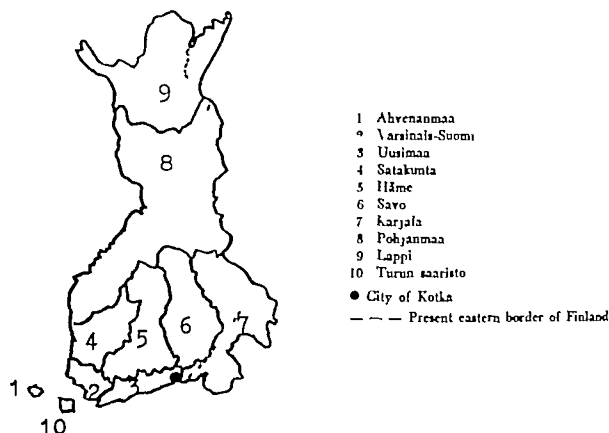
Provinces	sex	hyperleptorr	leptorr	mesorr	chamaerr	hyperchamaerr
Etelä Pohjanmaa	m	26.9	65.7	7.4	—	—
	f	42.9	53.1	4.0	—	—
Karjala	m	14.0	65.2	19.4	1.1	0.5
	f	22.8	61.7	15.7	[illegible]	—
Savo	m	9.4	49.5	33.3	6.6	1.2
	f	10.5	59.1	27.6	2.7	0.3
Uusimaa	m	13.1	56.3	29.0	1.1	0.5
	f	4	[illegible]	31.4	0.5	—
Satakunta	m	22.5	59.9	15.9	1.7	—
	f	27.8	58.1	11.7	1.9	0.5
Häme	m	7.7	60.1	23.6	8.4	0.2
	f	14.0	68.1	16.0	0	—
Turun saaristo	m	19.0	66.0	13.6	1.4	—
	f	16.6	73.8	8.7	1.0	—
Ahvenanmaa	m	8.7	66.0	24.9	—	—
	f	11.2	73.6	13.3	—	—
Varsinais-Suomi	m	5.4	63.0	29.6	2.0	—
	f	4.8	42.5	38.4	14.4	—

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Varsinais-Suomi	m	335	35 7	32.3	10.3	1 7
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	f	471	30 17	53 09	20 16	56 66 ± 0.338	67 10 ± 0.361
Karjala	m	724	33 07	53.37	22.33	65.80 ± 0 330	63 85 ± 0 444
	f	483	31 40	51.38	20 09	61.97 ± 0 376	63 92 ± 0.560
Savo	m	695	34.73	51.65	23.51	65.42 ± 0.510	67 71 ± 0 506
	f	376	30 99	47.38	21.92	65.79 ± 0 498	65 67 ± 0 624
Uusimaa	m	183	35.22	54.51	21.-1	65 29 ± 0 671	61 43 ± 0 741
	f	191	31.94	48 63	19 49	65.87 ± 0.509	61 41 ± 0 695
Satakunta	m	460	35.52	57.65	23.13	62 03 ± 0 423	66 21 ± 0.504
	f	646	31 78	52.57	20 40	61.03 ± 0.379	65 17 ± 0 449
Häme	m	426	35.55	58.72	22 63	66.59 ± 0 454	64.84 ± 0.500
	f	408	31.85	50 75	21 47	63 21 ± 0 411	63.28 ± 0.535
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Ahvenanmaa	m	182	34 83	54 22	19 78	64.80 ± 0.541	57 16 ± 0 759
	f	257	31 74	50.76	19.21	62 91 ± 0 418	60.35 ± 0.560
Varsinais-Suomi	m	335	35 27	53.50	22.35	66 63 ± 0 461	64 05 ± 0 596
	f	127	33 10	46 86	19 41	72 25 ± 0 958	58 76 ± 0 825

Table 4 Racial Division of the Finnish Nose (per cent)

Provinces	sex	hyper leptorr	leptorr	mesorr	chamaerr	hyper chamaerr
Etelä Pohjanmaa	m	26 9	65 7	7 4	—	—
	f	42 9	53.1	4 0	—	—
Karjala	m	14 0	65 2	19 4	1 1	0 3
	f	22 8	61 7	14 7	0 8	—
Savo	m	9 4	49 5	33 3	6 6	1 2
	f	10 3	59 1	27.0	2 7	0.3
Uusimaa	m	13 1	56 5	29 0	1 1	0 5
	f	4 2	63 9	31 4	0 5	—
Satakunta	m	22 5	59 8	14 9	3	—
	f	27 9	58 1	11 7	1 9	0.5
Häme	m	7 7	60 1	28 6	3 4	0.2
	f	14 0	68 1	16 0	2 0	—
Turun saaristo	m	19 0	66 0	13 6	1 4	—
	f	16 5	73 8	8 7	1 0	—
Ahvenanmaa	m	8 7	66 0	19	—	—
	f	11.3	73 8	15 5	—	—
Varsinais-Suomi	m	5 4	65 0	29 6	2 0	—
	f	4 8	42.2	38 4	14 4	—

In the beginning of this century the methods of measuring the nose were slightly different from modern methods.

In 1925 Y. J. Kajava gave directions as how to make anthropological examinations. He subdivided the nose into seven parts root, dorsum, tip alae, columella, nostrils and nares. The variations of the dorsum of the nose, for instance, were-

narrow ordinary broad, very concave, slightly concave, straight, slightly convex, very convex, irregular humpy long, medium, short. The septum was not included in his examinations.

Functions of the Nose
Physiological aspects

The well known functions of the nose are the sense of smell and the warming moistening and cleansing of air before it enters th lungs The nose has defence and reflex functions and it also forms a resonance chamber *in the formation of speech* and sound A great number of local and distant symptoms caused by impaired nasal ventilation can easily be explained *for instance* by the fact that the normal nose secretes one liter of water per day moisturizing to approximately 90 % humidity the 10 000 liters of air passing through it (Holloway 1971)

According to Ogura (1970) pulmonary resistance increases and compliance decreases with advancing degrees of nasal *obstruction* These are observed during oral as well as nasal breathing Ogura also found that abnormal preoperative values reverted to normal range four to six months following successful nasal surgery in about 85 per cent of the cases tested. Measurements of resistance in the air passages during oral breathing appear to be reliable criteria for determining the need for nasal surgery *(Ogura 1968)*

According to Uddstromer (1940) there are no mouth breathers among healthy persons while 56 % of people with septal deviation were mouth breathers. Exercise that did not make any of healthy people mouth breathers caused oral breathing in 88 % of persons with septal deviation. According to Drettner (1970) a high percentage of persons with septal deviation have an *absolute or relative* nasal respiratory insufficiency

Nasopulmonary and nasobronchial reflexes *have been assumed to* give an increased bronchial tone in cases of nasal obstruction which would *explain* the reversibility of pulmonary changes after successful operation on the nose (Drettner 1970) According to Sercer (1930) blowing of air *into one nostril* causes an expansion of the corresponding side of the thorax. This reaction is absent when the nasal *mucosa is anesthetized* He showed (Sercer 1952) that mechanical chemical or thermal stimulation of the nasal mucosa induced a nasobronchial reflex which was principally homolateral Sercer also pointed out a disturbance in the acid-base balance of the blood in patients with nasal obstruction, and suggested that this might be due to reduced pulmonary ventilation.

Methods of estimation of nasal functions (screening tests)

Olfaction

According to Strauss (1970) olfactory acuity decreases considerably with age. In normal breathing only about two per cent of the molecules reach the olfactory epithelium (Wit, 1967) Hagan (1967) has stated that test substances should include some which produce weak odors and some which produce strong odors and that the odors should be familiar and thus easily *identifiable*. His list of easily available and useful substances *includes the following progressing from weak odors to strong ones rosewater* coffee *cinnamon spirits of camphor* lavender oil oil of *cloves* and *peppermint extract*. In *addition some* substance to test the trigeminal sensation is necessary and for this purpose household ammonia is recommended If the patient denies any sensation from ammonia one may be rather suspicious of psychological or malingering problems.

In 1923 Proetz described a simple accurate clinical method of quantitative olfactometry He used ten different chemicals each of *them in ten different dilutions. The dilutions* were 1/4 1/2 1 2 3 5 10 25 50 and 100 times the perceivable concentration The purpose was not to identify the substance but to get an olfactory *sensation. Hansen* (1966) used the same kind of series of concentrations *His test* substances were acetophenone, methyl salicylate, menthol and scatol

Ottoson (1956) demonstrated a slow negative potential in the olfactory area when this was stimulated with smell saturated air. The reaction was called electro-olfactogram. Stimulation with odorless air did not cause a corresponding reaction. According to some scientists (Osterhammel, Terkildsen and Zilstorff 1969) this system, however applied to human beings, is difficult and unpractical from the clinical point of view. Van Dishoeck (1965) used ethanol, benzene, and camphor as testing substances. The choice of solvent was significant. For instance in sesam oil ethanol gave an olfactory stimulus in concentration 1:100 but when glycerol was used as the solvent the ratio had to be 1:250. v. Dishoeck's study of 700 patients did not show any effect of smoking or pregnancy on olfactory acuity. Allergy however almost always caused hyposmia.

A previous head injury has a significant effect on the results of testing the acuity of smell. After cranial injuries Leigh, (1943) found anosmia in 7.2 % and Sumner (1964) in 7.5 % of the patients. Caruso, Hagan and Manning (1969) also found that the incidence and degree of hyposmia increased with the degree of head trauma.

R pl ii

An adequate airway alone is not enough to guarantee good nasal health. There must be in addition sufficient resistance to both inspired and expired air currents. According to Rohrer (1915) 47 per cent of the total resistance of air passages is created in the nose. In later examinations (Ferris *et al.* 1964) even higher percentages have been presented. The resistance in the nose is provided by free ends of the medial and lateral crura, the cul-de-sac, the upper lateral valve, and the floor of the pyriform aperture (Hinderer 1971).

Several different methods of examination have been developed that aim at objective measurement of nasal conductivity (Spoor 1965). This section mainly concentrates on the rhinomanometrical methods and the results of the nasal respiration obtained by them.

A criticism that has been raised to most rhinomanometric techniques is that the values of data obtained in models, cadaver noses and nasal casts, as to the quantity of air passing through the nasal chamber per unit time, the pressure differences between the airway opening and the pharynx and the velocities of the air are not comparable to those obtained in the living nose because of the obviously great differences in the conditions of the experiments (Williams, 1970).

According to Cottle *et al.* (1965) the pressure of normal single breath of inspiration is about 6–15 mm/H_2O while that of expiration is usually 2–4 mm/H_2O less. Insufficiency in the valve area or atrophy of the mucosa decreases the pressure whereas the stenoses and obstructions in the valve area or vestibulum increase it. In a normal nose the pressure after shrinkage is higher in the upper nostril and lower in lower nostril (subject lying supine, turning his head alternately to left and right) than in upright position, because the upper lateral cartilage comes closer to the septum in the upper nostril and vice versa in the lower nostril. If stiffness occurs in the valve area this change does not take place. If the mucosa is not shrunk, the lower turbinates become swollen increasing the pressure in the lower nostril.

According to Cottle *et al.* (1965) nasal breathing pressures are studied in three ways: 1) rhino-sphygmo-manometry, 2) rhino-revma-sphygmo-manometry, 3) flow pressure relationship.

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In rhino-revma sphygmo-manometry the subject exhales or inhales through a flow

meter certain volumes of air per minute visually controlled.

In determining nasal flow pressure relationship flow and pressure can be recorded synchronously on a two channel recorder. The pressure is usually measured with a *manometer connected to a tube coming* from a nostril (anterior rhinomanometry). Measuring can also be done with the subject *having a* catheter *in his* mouth (v Dishoeck 1964) (posterior rhinomanometry). In this way the total pressure of both *nostrils* can be measured. Unfortunately this kind of posterior recording is only possible in about 50 % of patients due to the sensitive swallowing reflex (Kortekangas 1971).

The evaluation and diagnostic value of rhinomanometric results is based on empirical experiments with a great number of patients. Cottle (1968) reported a connection between certain aberrations of pressure *curves and certain pathological states* of noses. 1) Irregularities of breathing pattern amplitudes or frequency are often noted and usually *denote local derangements* within the nose. 2) A marked increase in breathing *pressure practically* always means a nasal obstruction and is especially predominant if the stenosis is in the area of a nasal valve. 3) If the pressure level at the height of expiration persists for 2 to 4 seconds this flat top aberration nearly always indicates the presence of the impaction of the septal spur or ridge in the posterior portion of the nose. 4) *Low inspiration* and *expiration* pressures *ranging* from 3 to 5 mm/H_2O or less are frequently found a) nasal chambers are abnormally wide b) patients are obese or asthenic c) there are localized mucosal involvements or an extreme sensitivity of the nasal mucosa. 5) After each completed breathing cycle there is a pause of 2—8 seconds during which there is no positive or *negative pressure*. Cottle has referred to this as »a mid cycle rest. *According* to him it is never a normal finding and is often seen in patients who have had difficult nasal breathing *for several years. In Cottle's* experience this aberration is often a sign of recent or old heart disease. *Rapidity* of breathing is often observed in children with adenoid obstruction or in adults with pulmonary disease. Uneven and unequal breathing patterns are often seen in emotionally disturbed people. The rate of nor*mal breathing ranges* from *10 to 18* times a minute.

Relations between Nasal Structure, Function, and Symptoms

A structural disproportion in the nose *creates a variety of* clinical symptoms which Cottle (1968) has described as the syndromes of nasal disharmony. For example, the white *person having the disproportions of a high* nasal index and low wide flattened nose, resembling that of negro type, will often manifest functional disturbances in breathing due to alteration of the direction and velocity of the air currents.

Disproportions of nasal structure may produce a great variety of symptoms and complaints referable to the nose such as referred pain considerable postnasal discharge, *recurrent sore throat cough etc. (Williams 1956) Nasal malformations often* result from injuries to the external pyramid *that may stop the growth or accelerate* it in the injured area. Thus the nose of a grownup person may be a most complicated combination of parts at different levels of development.

According to Hinderer (1964) the following symptoms occur most frequently in the abnormally wide nose crusting and occasional *bleeding stuffiness of the nose changes in* ability to smell and taste, indefinite facial pains headache postnasal discharge chronic *sore throat, persistent* cough recurrent stuffy ears, and chronic fatigue.

Ballooning of upper laterals decreases the sensation of the resistance to the inspired air and causes sensation of nasal blockage as

in atrophic rhinitis where again the airway is increased. Stretching of upper laterals by an excessively high septum produces a narrowing of the angle between the septum and the upper lateral and predisposes to a collapse of the cartilage on inspiration and produces a sensation of nasal obstruction. It has been called a »tension nose» and is accompanied by symptoms of nasal malfunction (Hinderer 1971). Returning of the upper lateral cartilages produces stiffening of the cartilage, stretching of the mucous membrane and impaired valve function (Cottle, 1960).

Even slight septal deviation can be of considerable importance if it is situated in the valve area. Septal spur or ridge in the most posterior part of the nose is near the region of the sphenopalatine ganglion causing many local and distant symptoms because of the irritation of the ganglion. Cottle (1960) has stated that the impaction is the state in which the nasal septum makes constant contact with the lateral wall of the nasal chamber despite shrinking of the mucosa by medication. If contact is broken by medication, the septal deviation is considered an obstruction.

A sleeping person changes his position many times each night. As stated by Masing and Horbachk (1969) these movements are mainly directed by the nose. In a lateral sleeping position a person is breathing more through the upper side of nasal cavity. If the upper nostril is obstructed, the congestion of the turbinates in the lower nostril makes breathing through the nose impossible and forces a person to sleep with the obstructed nostril downwards or breath through the mouth.

According to Ogura (1968) there was a definite tendency toward decreased one second vital capacity and maximum ventilatory volume of the lungs in abnormally obstructed noses. He used anatomical and physiological classification of nasal obstruction some features of which are presented below

— normal nose
0 straight septum, free airway
1 straight septum, slight enlargement of conchae
2 deviated septum with minimal intermittent nasal obstruction

— abnormal nose
3 deviated septum, fixed unilateral obstruction
4 anterior deviation of septum, impaction unilateral, upper lateral cartilage collapse unilateral, moderate obstruction
5 bilateral upper lateral cartilage collapse, moderate bilateral nasal obstruction
6 severe bilateral septal deviation, severe permanent bilateral nasal obstruction

Cinelli (1971) claims that it is also possible to draw conclusions about the traits of human personality from the shape of the nose.

Environmental Effects on Nasal Functions and Symptoms

Smoking habits

There are only a few remarks about the effect of smoking on nasal symptoms or functions in the literature (v Dishoeck, 1965 Hinderer 1971). On the other hand there are several remarks in the literature about the popularity of smoking. Physicians are a special group among smokers, because they are probably more aware of the dangers of smoking than other people. According to an examination made in Finland in 1969 (Vuori *et al.* 1972) only 23 per cent of the physicians in Finland were regular smokers (17 % of women and 24 % of men). Ten per cent smoked sometimes and 44 % had never smoked. In the 30—39 age group 26 per cent were regular smokers and in the 40—49 age group 25 per cent.

Hirvonen (1969) has collected from various examinations some percentages concerning the incidence of smoking in the 1960's of the schoolgirls in the fifth forms of the secondary schools in Helsinki 29.2 % were smokers, while of boys in the same forms 41.8 % smoked. 19 % of female and 47 %

meter certain volumes of air per minute visually controlled

In determining nasal flow pressure relationship flow and pressure can be recorded synchronously on a two channel recorder

The pressure is usually measured with a manometer connected to a tube coming from a nostril (anterior rhinomanometry) Measuring can also be done with the subject having a catheter in his mouth (v Dishoeck 1964) (posterior rhinomanometry) In this way the total pressure of both nostrils can be measured Unfortunately this kind of posterior recording is only possible in about 50 % of patients due to the sensitive swallowing reflex (Kortekangas 1971)

The evaluation and diagnostic value of rhinomanometric results is based on empirical experiments with a great number of patients Cottle (1968) reported a connection between certain aberrations of pressure curves and certain pathological states of noses 1) Irregularities of breathing pattern amplitudes or frequency are often noted and usually denote local derangements within the nose. 2) A marked increase in breathing pressure practically always means a nasal obstruction and is especially predominant if the stenosis is in the area of a nasal valve. 3) If the pressure level at the height of expiration persists for 2 to 4 seconds this flat top» aberration nearly always indicates the presence of the impaction of the septal spur or ridge in the posterior portion of the nose. 4) Low inspiration and expiration pressures ranging from 3 to 5 mm/H_2O or less are frequently found a) nasal chambers are abnormally wide b) patients are obese or asthenic, c) there are localized mucosal involvements or an extreme sensitivity of the nasal mucosa 5) After each completed breathing cycle there is a pause of 2—3 seconds during which there is no positive or negative pressure. Cottle has referred to this as a mid-cycle rest» According to him it is never a normal finding and is often seen in patients who have had difficult nasal breathing for several years. In Cottle's experience this aberration is often a sign of recent or old heart disease. Rapidity of breathing is often observed in children with adenoid obstruction or in adults with pulmonary disease. Uneven and unequal breathing patterns are often seen in emotionally disturbed people. The rate of normal breathing ranges from 10 to 18 times a minute.

Relations between Nasal Structure, Function, and Symptoms

A structural disproportion in the nose creates a variety of clinical symptoms which Cottle (1963) has described as the syndromes of nasal disharmony For example, the white person having the disproportions of a high nasal index and low wide flattened nose, resembling that of negro type, will often manifest functional disturbances in breathing due to alteration of the direction and velocity of the air currents

Disproportions of nasal structure may produce a great variety of symptoms and complaints referable to the nose such as referred pain considerable postnasal discharge recurrent sore throat, cough etc. (Williams 1956) Nasal malformations often result from injuries to the external pyramid that may stop the growth or accelerate it in the injured area. Thus the nose of a grownup person may be a most complicated combination of parts at different levels of development

According to Hinderer (1964) the following symptoms occur most frequently in the abnormally wide nose crusting and occasional bleeding stuffiness of the nose changes in ability to smell and taste, indefinite facial pains headache, postnasal discharge, chronic sore throat, persistent cough recurrent stuffy ears and chronic fatigue.

Ballooning of upper laterals decreases the sensation of the resistance to the inspired air and causes sensation of nasal blockage as

It has been found (Jeppesen and Winfeld, 1972) that the infants of primiparae, obviously due to a prolonged delivery had considerably more septal dislocations than those of multiparae. According to them, in a series of 907 newborn infants, who were all examined rhinologically the frequency of septal dislocations was 3 19 %. The frequency was not significantly higher in heavy newborn infants.

According to Hinderer (1971) among normally delivered white babies at least 5 per cent have marked deformities of the nose and 30 50 per cent have temporary flattening He has also stated that injuries during periods of rapid growth, i.e. 1 5 years and 10 15 years, cause greater disturbances.

of male students were smokers In the armed forces 64 6 % of the privates and 52.5 % of the officer cadets smoked. Of dock workers in the 25 49 age group 54 1 % were smokers.

Working conditions

Some studies have been made on the amount of subjective disadvantages in working conditions (Saari 1972) and about the effect of disadvantages on nasal symptoms or functions (Meurman 1948 Kereković 1971) For instance, of 3 886 people the following percentages said that they suffered from *certain disadvantages (Table 5)*

Table 5 Subjective disadvantages in working conditions according to Saari (per cent)

Disadvantage in working condition	continuous disturbing	temporary disturbing	not disturbing
High humidity	3	6	91
Temperature variations	15	26	59
Impurities in air (dust)	10	19	71
Chemicals (gaseous)	10	15	75
Draught	19	23	58

According to an examination (Lehto 1972) made by Tyoterveyslaitos (Institute of Occupational Health) in 1970 46 per cent of workers said that they suffered from a too high or too low temperature, 23 per cent suffered from humidity 20 per cent from impurities of air 22 per cent from chemicals and 65 per cent from draught.

Meurman (1948) has investigated the incidence of nasal symptoms in specific parts of the lime and cement factories in Finland Working conditions in these factories were very dusty Epistaxis was the complaint of 0.5 per cent of the mine and crusher house workers, 8 6 per cent of the cement workers and 39.5 per cent of the lime workers. The *chronic symptoms* were present in average as follows rhinitis 27 per cent, throat trouble 8 per cent cough 15 per cent, and impaired sense of smell 11 per cent. According to the slightly modified Proetz technique the sense of smell was *impaired in 44 4* per cent of 894 subjects tested

Growth of the Nose

Schultz (1920) found that the clinical nasal index was *different* between whites and negroes even in fetal life, decreasing in both races after birth At the age of five or six in the normal white child the nostrils have a tendency to narrow and increase in anteroposterior projection with a decrease in the clinical nasal index. In the colored child the nose becomes wider and more flattened and the nostrils become oval with an increase in the clinical nasal index.

Variations in the structure and function of the nose are usually caused by disturbance during the development of the nose or an injury that has happened later According to what Becker (1964) says in the textbook of human genetics, genetically based malformations of the nose are fairly rare.

According to Hillenbrandt (1933) disturbances in the growth can rather often be *found in the cartilaginous septum of fetus* This may be the reason for the later malformations. Leicher and Bergman (1958) have examined the inheritance of nasal deformities. If both the parents had a deviation of the septum it was also found in 80 % of their children If only one of the parents had the deviation it could be found in 55 per cent of the children and if the septums of both parents were straight, only 10 % of the children had a deviation According to Tepan (1970) the deviation of the septum may be inherited but the dislocation of the septum cannot be inherited He had examined 30 cases of dislocation of the septum. In 17 cases it was caused by an injury and in six cases by a difficult prolonged delivery

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URPOSE OF THE STUDY

he relation of nasal symptoms to structural isturbances has been recently emphasized by rhinologic surgeons. This study was lanned to estimate the incidence of nasal tructural disturbances among adults se ected by an equal interval sampling By sing some simple tests in addition to interviews about relevant matters, correlations of nasal symptoms and signs were studied. In the light of the facts revealed this study attempts to answer the following questions

1 Is the way of selecting test subjects for this study acceptable?

2 What is the incidence of nasal disorders among unselected adult population?

3 Are there any special racial features of the nose in this material?

4 How reliable are the methods of testing used in this study?

5 What are the norms for the rhinomanometric values obtained in this study?

6 Which is the incidence of significant correlations between nasal symptoms and signs in relation to general health and environmental circumstances?

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6 Which is the incidence of significant correlations between nasal symptoms and signs in relation to general health and environmental circumstances?

MATERIAL AND METHODS OF THE STUDY

Selection of Subjects for the Study

Two hundred people in anthropological age (from 25 to 50 years) were randomly selected for this examination by equal interval sampling from the official register of the town of Kotka (33 000 inhabitants). They were invited by letter and informed about the examination of the nose and upper respiratory system. The test was said to take one hour and to be free. The reasons for those 38 who did not attend were, two were not willing, nine peole did not come because their work did not permit it, because they were ill or because their addresses were unknown and one was dead. In twenty-six cases the reason for absence remained obscure.

Table 6 Availability of subjects chosen by sampling

	women	men	total
Examined	91	71	162
Absent	18	20	38
	109	91	200

Methods Applied in Examination of Each Subject

Clinical examination and filling in the questionnaire

The questionnaires were filled in by the author who also took the photographs and carried out the measurements and tests. Both the symptoms and signs related to the subjects of this investigation were transferred to a certain form suitable for computer analysis. Every investigation started with an inquiry including 61 questions, about background variables (page 25). The subjects were asked for their opinions and encouraged to be spontaneous. The classification of the answers into 3—7 statistical groups according to the frequency or severity of symptoms was decided by the author. The clinical description consisted of 6 olfactory and 30 rhinomanometrical measurements, 8 indices were measured and checked by photography. In addition 48 evaluations were made of the structure and / or state of pyramid, septum, turbinates, skin, mucous membrane, nasopharynx, secretion of the nose, and phonation.

Measuring the indices

The clinical nasal index and the tip index were selected because of their supposed clinical importance (Hinderer 1964) as a means of evaluating the structure of the nose in this study (Fig 1). The salience index was also included.

$$\text{Clinical nasal index} = \frac{100 \times \text{maximum width between pyriform crests}}{\text{height of the nose}}$$

$$\text{Tip index} = \frac{100 \times \text{width at level of apex of nostrils}}{\text{width at widest expansion of alae}}$$

$$\text{Salience index} = \frac{100 \times \text{greatest projection of the dorsum}}{\text{projection of the tip}}$$

measurements. On the basis of these results the minute volume was determined at rest, *after exercise*, and during maximal nasal ventilation. During the examination the subject's nose was under an airtight diver's mask. Master Step was used as a form of exercise. During the period of thirty seconds the subject stepped 15 times on to a bench that was 40 cm high. The measurement was taken one minute after the beginning of the exercise. Finally the maximal nasal ventilation was examined and here again the diver's mask was used. The subject was asked to breathe maximally through both nostrils. The subject was in a sitting position during the test.
To determine the norms for the rhinomanometric readings, the limiting values of the middlemost 50, 60 and 80 per cent were determined from inspiration and expiration pressures as well as from the volume of maximal nasal breathing for both sexes separately.

Vitalogram

The vital capacity of the lungs (VC), the maximal ventilatory volume (MVV) and the volume of forced expiration at 0.5 seconds (FEV .5) were determined by vitalogram (Vitalograph ®). These values can be read according to the age and height of the subject from the nomogram (Kory et al. 1961). Maximal ventilatory volume is obtained from the equation FEV .5 x 40 (Kennedy 1953, Cara, 1953). The vitalogram test was made three times by every subject, and the best reading was accepted.

Tension test

The degree of the tension of the nose was examined by using a tension test. The subjects were asked to say oo [u]; at the same time the degree of coming down of the tip was observed. If there was no movement of the tip, the result was negative.

Statistical Methods

The effects of background or environmental factors (i.e. background or independent variables) on the nasal symptoms and results of functional tests (i.e. dependent variables) were analyzed statistically.

Independent variables

The following items were used as background variables: sex, age, height, working conditions, previous operations, heredity, incapacitating diseases, previous diseases, recent medicines, smoking habits, sleeping position, nasal indices, skin and mucous membranes, appearance of external nose, nasal septum, vestibulum, and valve area.

Dependent variables

Nasal symptoms (= nasal symptom complex) and results of olfactory, trigeminal, rhinomanometric, and tension tests (= nasal sign complex) were used as dependent variables. A vitalogram examination was used for the comparison of nasal and pulmonary functions.

Nasal symptom complex

Eleven of the nasal symptoms of this study were applied to characterize unsatisfactory function of the nose (table 25). According to the intercorrelations of these symptoms a nasal symptom complex was formed on the basis of the following five items: dryness of throat, sneezing, postnasal discharge, snoring, and mouth breathing (table 26). Every item ranged from 1 to 3 points (for instance: continuous = 1, frequent = 2, seldom or never = 3). The total number of points (5—15) changes with the presence or absence of symptoms and can be used as a variable in correlation studies.

Olfactory complex

An olfactory complex of four items (olfactory stimuli I and II, right and left nostril

The width of the nose is determined by feeling the lateral edges of the pyriform crest through the skin and measuring the distance between them The height is measured *from nasale to subnasale*.

The measurements in tip index are the width of the base of the nose on the level of apex of each nostril and the widest expansion of the alae. The projection of the bony dorsum is measured from the baseline to the greatest prominence of the dorsum with the ruler *held perpendicular to the dorsum* The projection of the tip is measured from the alar facial groove to the tip of the nose (Cottle 1960)

Photography

Four slides a frontal view two lateral views and a base view were taken of every subject against a dark green background. A scale was enclosed in the photographs to make it possible to enlarge the slides to the standard size. In frontal view the same amount of each ear was visible and the Frankfort Horizontal line (Hinderer 1971) from the tragus to the suborbital was parallel to the floor In lateral views also the *Frankfort line was horizontal and only one* eyebrow was visible In base view the head was bent back until the tip of the nose reached the line between the eyebrows The slides were projected on the screen for measuring indices

Olfactory and trigeminal tests

The aim was to determine roughly the acuity of the sense of smell of the *subjects*. For that purpose two different olfactory stimuli (coffee = O_1 and cocoa = O_2) and one trigeminal stimulus (vinegar = T) were used Each nostril was tested separately The mucous membrane had not been shrunk at the beginning of the examination. The narrower nostril was always tested first If there was any difference between the nostrils in acuity while testing by the first stimulus the following tests were first made to the less efficient nostril The test substances were renewed weekly to keep them fresh and they were familiar to everbody

Rhinomanometry

Equipment

The rhinomanometric apparatus consisted of pneumotachograph model Fleich AM 282 Elema transducers EMT 32 and EMT 33 Elema amplifier EMT 31 Elema writer *Mingograph 34 with an inbuilt volume in*tegrator and a micromanometer for calibration.

Pressure tests

First an anterior rhinomanometry was performed while the subject was supine. Inspi*ratory and expiratory pressures* were recorded separately from the right and left nostril The opposite nostril was closed air tightly with a nozzle which did not distort the septum or the nostril under examination The same *examination was renewed after* the mucous membrane had been shrunk After that the breathing pressures were examined turning the head of the subject alternately with right and left side of the nose up and the decrease in *the breathing* pressure caused by dilatation of the upper nostril was measured at the same time The averages of 4—5 successive deviations above or below the baseline of the rhinogram were determined to represent respectively expiration or inspiration of the subject.

Flow tests

Flow tests were performed separately after pressure tests The frequency of nasal breathing and the volume of a single breath were measured from a volume curve Also here 4—5 successive deviations were used as a basis for measurements The lower edge of the line was *always used as the point of*

measurements. On the basis of these results the minute volume was determined at rest, after exercise, and during maximal nasal ventilation. During the examination the subject's nose was under an airtight diver's mask. Master Step was used as a form of exercise. During the period of thirty seconds the subject stepped 15 times on to a bench that was 40 cm high. The measurement was taken one minute after the beginning of the exercise. Finally the maximal nasal ventilation was examined and here again the diver's mask was used. The subject was asked to breathe maximally through both nostrils. The subject was in a sitting position during the test.
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An olfactory complex of four items (olfactory stimuli I and II, right and left nostril

tested separately) was used for a combined olfactory variable Every item ranged from 1 to 3 points (no sensation = 1 positive sensation = 2 stimulus identified = 3) Here again the total number of points (4—12) obtained by the subject was used as a basis for correlation studies

Trigeminal complex

A trigeminal complex of two items (stimulus in right and left nostril) was used for a combined trigeminal variable ranging from 1 to 3 points according to the same system as olfactory items (no sensation = 1 positive pungent sensation = 2 identified = 3) From 2 to 6 points could be obtained by one person.

Pressure complex

To make the results of nasal pressure changes applicable for correlation studies the averages of pressures in all groups (no medication, after shrinkage inspiration expiration right nostril and left nostril) were evaluated also taking age into consideration In every group the pressures of the subject were compared to the mean value and according to the percentage deviation from it the results ranged from 1 to 3 points Low quartile = 1 middlemost 50 per cent = 2 and high quartile = 3 points.

Flow complex

The mean volumes of maximal nasal ventilation were grouped according to the age and height of the subjects Percentage deviatons of the volume readings from the averages were divided into quartiles, which were used as in the case of the pressure complex.

Correlation studies

To examine the correlations of nasal symptoms and signs frames of reference were formed using the background variables and dependent variables of this study as a basis Significant positive or negative correlations were expressed respectively with signs + or — and the degree of significance was expressed by * as an exponent of the sign Non significant correlation was expressed by the sign o The following levels of significance were chosen.

$0.05 \geq p > 0.01$
$0.01 \geq p > 0.001$
$0.001 \geq p$

significant level for 162 cases is r = 154
91 r = .205
71 r = .232
162 r = .202
91 r = .267
71 r = .302
162 r = .256
91 r = .335
71 r = .350

RESULTS

Background Variables

Sex age and height

The 162 subjects of this study were investigated in relation to all variables. There were 91 women and 1 men among the subjects.

The distribution of the age of the subjects is given in table 7. The ages are divided into three approximately equal groups to permit correlation anlysis. The distribution into four height groups is given in table 8, and the mean height values in different age groups are presented in table 9. The tendency of increasing height among younger people could be seen.

Table 7 Distribution of subjects into age groups and mean ages (years)

Age years		per cent	Mean age (years)	
25	34	36 6	Male	37 9 years
35	49	28 0	Female	37 1
41	50	35 4	Total	37 4

Table 8 Distribution of subjects into height groups and mean heights (cm)

Height cm		per cent	Mean height (cm)	
	160	20 5	Male	174 9 cm
161	170	42 9	Female	162 1 cm
171	180	30 4	Total	167 7 cm
181		6		

Table 9 Mean height of the subjects in different age groups

Age years		Mean height cm	
		Male	Female
25	34	176 8	163 2
35	40	175 8	16. 0
41	50	1 5 6	161 1

Working conditions

The opinions of the test subjects about their working conditions are analysed in table 10. For retired subjects (five) and housewives (17) the living surroundings were taken to represent their working conditions. 16 per cent were mainly outdoor workers 61 per cent were mainly indoor workers, and 15 per cent had about equal amounts of out door and indoor work.

Table 10 Subjective opinion of the subjects about their working conditions (per cent)

Working condition	Continuously disturbing	Temporarily disturbing	Not disturbing
High humidity	4	9	87
Temperature variations	7	30	63
Impurities in air (dust)	15	25	60
Chemicals (gaseous)	6	12	82
Draught	9	36	55

In table 11 the incidence of outdoor or in door work is correlated to the amount of subjective disadvantages in working conditions.

Table 11 Correlation of working conditions to the subjective disadvantages[1])

Disadvantage in working conditions	Outdoor/indoor work
High humidity	O
Temperature variations	+
Impurities in air (dust)	+
Chemicals (gaseous)	+
Draught	O

[1]) N = 162 see page 24

tested separately) was used for a combined olfactory variable. Every item ranged from 1 to 3 points (no sensation = 1 positive sensation = 2 stimulus identified = 3) Here again the total number of points (4—12) obtained by the subject was used as a basis for correlation studies

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significant level for 16 cases is r = [illegible]
91 r = .205
71 r = .232
16 r = [illegible]
91 r = .267
71 r = .302
16 r = [illegible]
81 r = .339
71 r = .350

Table 13 Incidence of previous diseases of the subjects related to their nasal or pulmonary symptoms and signs (per cent)

Dyspnea	
— continuous	1
— temporary	7
— after exercise	8
— never	84
Allergic symptoms	
— frequent	6
— seldom	33
— never	60
Heart symptoms	
— coronary artery disease	4
— pulse rate irregularities	7
— none	89
Sinusitis	
— positive irrigation	9
— diagnosed by X-ray	5
— suspected because of symptoms	10
— no sinusitis	8
Head injuries	
— unconscious > 24 hours	2
— unconscious > 1/2 hours	3
— momentarily	17
— no previous history	78
Skull fracture	
— unconscious > 24 hours	1
— > 1/2 hours	1
— no skull fracture	98
Nose fracture/contusion	
— fracture	2
— contusion	7
— no nasal injury	91
Frequency of rhinitis	
— continuous	12
— common	51
— rare	37
Type of rhinitis	
— seasonal	3
— infectious	67
— vasomotor	25
— not specified	5
Quality of secretion	
— purulent, mucous	51
— watery	36
— obstruction without secretion	
Obstruction of the nose	
— mainly on the right side	6
— mainly on the left side	4
— on both sides	23
— no obstruction	67
Headache	
— continuous	3
— frequent	25
— seldom	31
— hardly ever	41

Recent medicines

Long term usage of medicines can be assumed to have some effect on the functions of the organism The usage of medicines (during five recent years) examined in this study has however in many cases been temporary so that the results are not the same as they were during treatment with antibiotics, antihistamines cortisone or nose drops. Oral contraceptives which are very commonly used among women, and antihypertensives are, however used during long periods and regularly (table 14)

Table 14 Recent usage of medicines among the test subjects (per cent)

Medicine	Frequent	Seldom	Never
Antibiotics	9	67	24
Antihistamines	3	3	94
Cortisone	1	4	95
Nose drops	1	34	65
Oral contraceptives (women)	25	22	53
Antihypertensives	2	2	96

Smoking habits

47.5 per cent of all the subjects were smokers 70.4 per cent of the men and 29 per cent of the women smoked The readings are relatively high compared to the results obtained by Vuori *et al* (1972) and Hirvonen (1969) Because about one half of the subjects were non-smokers, the effect of smoking on the symptoms and signs of the nose will be examined carefully in this study A more detailed analysis of smoking habits can be seen in tables 15 and 16.

Table 15 Amount of smoking (per cent)

> one packet*) daily	6
about one packet daily	21
about 1/2 packet daily	15
some cigarettes daily	7
non-smoker	43

*) one packet contains 20 cigarettes

Table 16 Duration of smoking (per cent)

> 15 years	25
5 15 years	16
< 5 years	3
non-smoker	53

Outdoor work was experienced significantly disadvantageous as far as temperature variations and the presence of impurities and chemicals in inspired air were concerned. High humidity and draught on the other hand were equally disturbing in both indoor and outdoor work.

Previous operations

Although the subjects were randomly selected none of them had had a previous septum or pyramid operation. One had had a maxillary sinus operation, polypi had been removed from two persons, and four of them had had a turbinate operation. Adenoidectomy had been made in 4.9 per cent and tonsillectomy in 15.4 per cent.

Heredity

The subjects were asked about the incidence of asthma, allergic rhinitis, chronic infectious rhinitis, and heart diseases among close relatives (grandparents, parents, brothers and sisters and children) (table 12). The subjects seemed to have a very clear idea about the heart diseases of their relatives but the notes about nose troubles among the relatives were more or less guesses. Apparently only the incidence of heart diseases and asthma can be used reliably while examining intercorrelations of heredity and nasal symptoms and signs.

Table 12. The incidence of nasal respiratory and heart diseases among close relatives (per cent)

Symptoms	Frequent	Occasional	None
Rhinitis chr	0	5	95
Rhinitis allerg	1	8	91
Asthma	3		75
Heart disease	1	30	55

Incapacitating diseases

Eleven of the subjects were suffering from a serious disease that obviously lowered their functional capacity. The diagnoses were: 1 multiple sclerosis, 1 pulmonary emphysema, 1 hypertension, 1 pulmonary silicosis, 1 hypothyroidism, 1 pulmonary tuberculosis, 1 coronary artery disease, 1 hemiplegia, 1 epilepsy and 2 diabetes. In addition to these one case of laryngeal cancer was disclosed by this examination. Incapacitating diseases of the subjects were sporadic and most of them could not be considered to have any effect on nasal or pulmonary functions.

Previous diseases

Table 13 gives the frequencies of the previous diseases related to the symptoms and signs of the nose and upper respiratory system as reported by the subjects.

The number or frequency of previous diseases and symptoms according to table 13 was in some cases so high that statistical treatment was possible. The subjects had had some degree of dyspnea in 16 %, allergic symptoms in 31 %, heart symptoms in 11 %, sinusitis in 24 %, unconsciousness caused by head injuries in 26 %, nasal injuries in 9 %, chronic rhinitis in 43 % and headache in 59 %.

Six of the nasal injuries (table 13) had taken place during the age of growth and eight after it. The effect of injuries on the later development of the nose could not, however, be examined because the cases were so few. None of the subjects had a nasal deformity caused by freezing, burning or illness. 19 subjects had weighed at birth more than four kg, 114 less than that and 29 did not know their weight at birth. Two of the subjects had been delivered through a Caesarean section, 155 normally and five did not know how they had been delive-

Table 13 Incidence of previous diseases of the subjects related to their nasal or pulmonary symptoms and signs (per cent)

Dyspnoea	
— continuous	1
— temporary	7
— after exercise	8
— never	84
Allergic symptoms	
— frequent	6
— seldom	25
— none	69
Heart symptoms	
— coronary artery disease	4
— pulse rate irregularities	7
— none	89
Sinusitis	
— positive irrigation	9
— diagnosed by X-ray	6
— suspected because of symptoms	10
— no sinusitis	78
Head injuries	
— unconscious > 24 hours	2
— unconscious > 1/2 hours	5
— momentarily	17
— no previous history	76
Skull fracture	
— unconscious > 24 hours	1
— > 1/2 hours	1
— no skull fracture	95
Nose fracture/contusion	
— fracture	2
— contusion	7
— no nasal injury	91
Frequency of rhinitis	
— continuous	12
— common	31
— rare	57
Type of rhinitis	
— seasonal	8
— infectious	67
— vasomotor	23
— not specified	5
Quality of secretion	
— purulent, mucous	51
— watery	26
— obstruction without secretion	
Obstruction of the nose	
— mainly on the right side	6
— mainly on the left side	4
— on both sides	23
— no obstruction	67
Headache	
— continuous	
— frequent	8
— seldom	25
— hardly ever	31
	41

Recent medicines

Long term usage of medicines can be assumed to have some effect on the functions of the organism. The usage of medicines (during five recent years) examined in this study has, however in many cases been temporary so that the results are not the same as they were during treatment with antibiotics, antihistamines, cortisone or nose drops. Oral contraceptives which are very commonly used among women, and anti hypertensives are, however used during long periods and regularly (table 14).

Table 14 Recent usage of medicines among the test subjects (per cent)

Medicine	Frequent	Seldom	Never
Antibiotics	9	67	24
Antihistamines	1	5	94
Cortisone	1	4	95
Nose drops	1	34	65
Oral contraceptives (women)	25	22	53
Antihypertensives	2	2	96

Smoking habits

47.5 per cent of all the subjects were smokers. 70.4 per cent of the men and 29.7 per cent of the women smoked. The readings are relatively high compared to the results obtained by Vuori *et al* (1972) and Hirvonen (1969). Because about one half of the subjects were non-smokers the effect of smoking on the symptoms and signs of the nose will be examined carefully in this study. A more detailed analysis of smoking habits can be seen in tables 15 and 16.

Table 15 Amount of smoking (per cent)

> one packet[1]) daily	
about one packet daily	6
about 1/2 packet daily	21
some cigarettes daily	13
non-smoker	7
	53

[1]) one packet contains 20 cigarettes

Table 16 Duration of smoking (per cent)

> 15 years	
5 15 years	28
< 5 years	16
non-smoker	3
	53

Outdoor work was experienced significantly disadvantageous as far as temperature variations and the presence of impurities and chemicals in inspired air were concerned. High humidity and draught on the other hand were equally disturbing in both indoor and outdoor work.

Previous operations

Although the subjects were randomly selected, none of them had had a previous septum or pyramid operation. One had had a maxillary sinus operation, polypi had been removed from two persons, and four of them had had a turbinate operation. Adenoidectomy had been made in 4.9 per cent and tonsillectomy in 15.4 per cent.

Heredity

The subjects were asked about the incidence of asthma, allergic rhinitis, chronic infectious rhinitis and heart diseases among close relatives (grandparents, parents, brothers and sisters and children) (table 12). The subjects seemed to have a very clear idea about the heart diseases of their relatives but the notes about nose troubles among the relatives were more or less guesses. Apparently only the incidence of heart diseases and asthma can be used reliably while examining intercorrelations of heredity and nasal symptoms and signs.

Table 12. The incidence of nasal, respiratory and heart diseases among close relatives (per cent)

Symptoms	Frequent	Occasional	None
Rhinitis, inf.	0	5	95
Rhinitis, allerg.	1	8	91
Asthma	3	2	5
Heart disease	1	30	55

Incapacitating diseases

Eleven of the subjects were suffering from a serious disease that obviously lowered their functional capacity. The diagnoses were: 1 multiple sclerosis, 1 pulmonary emphysema, 1 hypertension, 1 pulmonary silicosis, 1 hypothyroidism, 1 pulmonary tuberculosis, 1 coronary artery disease, 1 hemiplegia, 1 epilepsy and 2 diabetes. In addition to these one case of laryngeal cancer was disclosed by this examination. Incapacitating diseases of the subjects were sporadic and most of them could not be considered to have any effect on nasal or pulmonary functions.

Previous diseases

Table 13 gives the frequencies of the previous diseases related to the symptoms and signs of the nose and upper respiratory system as reported by the subjects.

The number or frequency of previous diseases and symptoms according to table 13 was in some cases so high that statistical treatment was possible. The subjects had had some degree of dyspnea in 16 %, allergic symptoms in 31 %, heart symptoms in 11 %, sinusitis in 24 %, unconsciousness caused by head injuries in 26 %, nasal injuries in 9 %, chronic rhinitis in 43 % and headache in 59 %.

Six of the nasal injuries (table 13) had taken place during the age of growth and eight after it. The effect of injuries on the later development of the nose could not, however, be examined because the cases were so few. None of the subjects had a nasal deformity caused by freezing, burning or illness. 19 subjects had weighed at birth more than four kg, 114 less than that and 29 did not know their weight at birth. Two of the subjects had been delivered through a Caesarean section, 155 normally and five did not know how they had been delivered.

Table 13 Incidence of previous diseases of the subjects related to their nasal or pulmonary symptoms and signs (per cent)

Dyspnea	
— continuous	1
— temporary	7
— after exercise	8
— never	84
Allergic symptoms	
— frequent	6
— seldom	23
— none	80
Heart symptoms	
— coronary artery disease	4
— pulse rate irregularities	7
— none	89
Sinusitis	
— positive irrigation	9
— diagnosed by X-ray	5
— suspected because of symptoms	10
— no sinusitis	76
Head injuries	
— unconscious > 24 hours	2
— unconscious > 1/2 hours	5
— momentarily	17
— no previous history	76
Skull fracture	
— unconscious > 24 hours	1
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— no skull fracture	83
Nose fracture/contusion	
— fracture	2
— contusion	7
— no nasal injury	91
Frequency of rhinitis	
— continuous	12
— common	31
— rare	57
Type of rhinitis	
— seasonal	5
— infectious	67
— vasomotor	5
— not specified	5
Quality of secretion	
— purulent, mucous	51
— watery	26
— obstruction without secretion	
Obstruction of the nose	
— mainly on the right side	6
— mainly on the left side	4
— on both sides	23
— no obstruction	67
Headache	
— continuous	1
— frequent	25
— seldom	31
— hardly ever	41

Recent medicines

Long term usage of medicines can be assumed to have some effect on the functions of the organism. The usage of medicines (during five recent years) examined in this study has, however in many cases been temporary so that the results are not the same as they were during treatment with antibiotics, antihistamines, cortisone or nose drops. Oral contraceptives, which are very commonly used among women, and antihypertensives are, however used during long periods and regularly (table 14)

Table 14 Recent usage of medicines among the test subjects (per cent)

Medicine	Frequent	Seldom	Never
Antibiotics	9	67	4
Antihistamines	3	3	84
Cortisone	1	4	0
Nose drops	1	31	65
Oral contraceptives (women)	25	22	65
Antihypertensives	2	2	96

Smoking habits

47.5 per cent of all the subjects were smokers. 70.4 per cent of the men and 29.7 per cent of the women smoked. The readings are relatively high compared to the results obtained by Vuori *et al* (197*) and Hirvonen (1969). Because about one half of the subjects were non-smokers, the effect of smoking on the symptoms and signs of the nose will be examined carefully in this study. A more detailed analysis of smoking habits can be seen in tables 15 and 16

Table 15 Amount of smoking (per cent)

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some cigarettes daily	7
non-smoker	53

[1]) one packet contains 20 cigarettes

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Although the subjects were randomly se lected none of them had had a previous septum or pyramid operation One had had a maxillary sinus operation polypi had been removed from two persons and four of them had had a turbinate operation Ade noidectomy had been made in 4 9 per cent and tonsillectomy in 15 4 per cent

Heredity

The subjects were asked about the incidence of asthma allergic rhinitis chronic infec tious rhinitis, and heart diseases among close relatives (grandparents parents broth ers and sisters and children) (table 12) The subjects seemed to have a very clear idea about the heart diseases of their rela tives but the notes about nose troubles among the relatives were more or less guesses Apparently only the incidence of heart diseases and asthma can be used reliably while examining intercorrelations of heredity and nasal symptoms and signs

T a b l e 1 2 The incidence of nasal respira tory and heart diseases among close rela tives (per cent)

Symptoms	Frequent	Occasional	None
Rhinitis chr	0	5	95
Rhinitis allerg	1	8	91
Asthma	3	2	75
Heart disease	1	30	58

Incapacitating diseases

Eleven of the subjects were suffering from a serious disease that obviously lowered their functional capacity The diagnoses were 1 multiple sclerosis 1 pulmonary emphysema 1 hypertension, 1 pulmonary silicosis 1 hypothyroidism 1 pulmonary tu berculosis 1 coronary artery disease 1 he miplegia 1 epilepsy and 2 diabetes In addition to these one case of laryngeal cancer was disclosed by this examination. Incapacitating diseases of the subjects were sporadic and most of them could not be considered to have any effect on nasal or pulmonary functions

Previous diseases

Table 13 gives the frequencies of the pre vious diseases related to the symptoms and signs of the nose and upper respiratory sys tem as reported by the subjects

The number or frequency of previous diseases and symptoms according to table 13 was in some cases so high that statistical treatment was possible The subjects had had some degree of dyspnea in 16 %, aller gic symptoms in 31 % heart symptoms in 11 % sinusitis in 24 % unconsciousness caused by head injuries in 26 % nasal in juries in 9 %, chronic rhinitis in 43 % and headache in 59 %

Six of the nasal injuries (table 13) had taken place during the age of growth and eight after it. The effect of injuries on the later development of the nose could not however be examined because the cases were so few None of the subjects had a nasal deformity caused by freezing burning or illness 19 subjects had weighed at birth more than four kg 114 less than that and 29 did not know their weight at birth Two of the subjects had been delivered through a Caesarean section, 155 normally and five did not know how they had been delivered

Table 21 Appearance of the external nose (per cent)

Profile of the nose	
— fairly straight	42
— concave	49
— convex	8
— deformed	1
Pyramid	
— tilted to the right	4
— tilted to the left	4
— C-shaped deviation	8
— reversed -deviation	4
— straight and in midline	82
Tip	
— deviation to the right	2
— deviation to the left	9
— no deviation	89
Alar folds	
— marked	25
— weak	75
Naso-labial angle	
— acute	4
— 85 95°	87
— obtuse	9
Nostrils	
— deformed	1
— narrow	3
— round	14
— elliptical	82

Nasal septum

When the septum was examined special attention was paid to the deviations and their relationship with the lateral wall. The location of obstructions and impactions were determined. There were no subjects with septal perforations in this study

Dislocation of the caudal end of the septum could be found in 17 % obstructing septum in 10 %, impacting septum in 14 % and considerable deviation of the septum in 11 % of the subjects (Table 22) This examination supports the view that septal deviation occurs more frequently on the left than on the right.

Table 22 Incidence of septal deformities among subjects (per cent)

Caudal septum	
— in right vestibulum	10
— in left vestibulum	7
— in the midline	83
Obstruction (16 cases)	
— anterior	6
— posterior	4
— to the right	4
— to the left	6
— no obstruction	90
Impaction (23 cases)	
— anterior	
— posterior	12
— to the right	8
— to the left	6
— to the middle turbinate	
— to the inferior turbinate	12
— no impaction	85
Septal deviation (77 cases)	
— considerabl to both sides	1
— considerabl to the right	4
— considerable to the left	6
— moderate to the right	14
— moderate to the left	23
— no apparent deviation	5.

According to this examination no correlation could be found between the most prevalent sleeping position (table 17) and presence of impaction, obstruction or considerable deviation of the septum.

The influence of septal pathology is discussed in more detail in table 23 The low incidence of nasal pathology in this material, as can be expected in a random sample, limits the validity of statistical analysis of the correlations between symptoms and signs. Regarding obstruction and impaction some comparisons were, however made with the percentages of the whole material.

Ogura s (1968) classification (page 15) of the state of obstruction in the nose has not been used in this study because the effect of separate intranasal deformities on nasal symptoms and signs has been of particular interest.

Sleeping position

Many of the subjects had a clear idea of their most prevalent (often also the only possible) sleeping position (table 17)

T a b l e 1 7 Most prevalent sleeping position of the subjects (per cent)

On the right side	11
On the left side	8
Supine	8
Prone	16
Half Sitting	1
Many positions possible	56
Cannot tell	1

Nasal indices

Average values of the clinical nasal index (NI) the tip index (TI) and the salience indices (SI) as well as the index values obtained by photography are given in table 18 Attempts to classify noses into racial groups by using the salience index (table 19) or the clinical nasal index and the tip index (table 20) give quite different results The indices obtained by photography are systematically lower than those obtained by measurings on the subjects

T a b l e 1 8 Average index values of the subjects

	NI	TI	SI dx	SI si
Men	53 3	75 0	69.9	60.8
Women	5 1	76 0	63 9	63 6
Total	5 6	75 6	65.2	65 0
Photography	50 4	69.2	61.9	61.3

T a b l e 1 9 Racial distribution of the subjects according to salience index (SI)

	SI dx %	SI I %
<55	4.9	3 7
55—65 = leptorrh ne	45 1	43.8
>65	50 0	5 5

T a b l e 2 0 Comparison of racial distribution according to TI and NI

		Clinical nasal index %			
		Leptorr	Mesorr	Platyrr	Total
Tip index %	Leptorr	43	1	—	44
	Mesorr	29	5	1	35
	Platyrr	90	1	—	1
	Total	9	7	1	100

Skin and mucous membrane

Pathological changes in the skin of the nose were small scars in 4 9 % vascular changes in 0 6 % atrophy in 1.9 % and dermatitis in 2.5 % of subjects. The scars were in all cases due to a trauma In two out of three cases the atrophy of the skin was connected with a positive tension test.

In mucous membranes the changes were much more frequent atrophy in 14 % hypertrophy in 10 % and inflammation in 7 % of the subjects. Mucous secretion was observed in 29 and watery secretion in the noses of 9 per cent of the subjects. Notes about the state of mucous membranes were, however based on subjective opinions of the author and not on any specific examination

Appearance of the external nose

The various details of the shape and structure of the external nose, which were examined are given in table 21

Asymmetry of the nasal pyramid was found in 18 % asymmetry of the tip in 11 % abnormally acute or obtuse naso labial angle in 13 % and other than elliptical form of the nostrils in 18 % of the subjects (table 21) In addition to that the nostrils were asymmetrical in 12 per cent the columella was hanging in 5 retracted in 2 short in 1 long in 3 and oblique in 3 per cent of the subjects

Table 21 Appearance of the external nose (per cent)

Profile of the nose	
— fairly straight	4
— concave	43
— convex	8
— deformed	1
Pyramid	
— tilted to the right	4
— tilted to the left	4
— C-shaped deviation	6
— reversed -deviation	4
— straight and in midline	82
Tip	
— deviation to the right	2
— deviation t the left	9
— no deviation	89
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— acute	4
— 85 95°	87
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— deformed	1
— narrow	3
— round	14
— elliptical	82

Table 22 Incidence of septal deformities among subjects (per cent)

Caudal septum	
— in right vestibulum	10
— in left vestibulum	7
— in the midline	83
Obstruction (16 cases)	
— anterior	6
— posterior	4
— to the right	4
— to the left	6
— no obstruction	90
Impaction (23 cases)	
— anterior	2
— posterior	12
— t the right	8
— to the left	6
— to the middle turbinate	2
— to the inferior turbinate	12
— no impaction	86
Septal deviation (77 cases)	
— considerable to both sides	1
— considerabl to the right	4
— considerable to the left	6
— moderate to the right	14
— moderate to the left	23
— no apparent deviation	52

Nasal septum

When the septum was examined special at tention was paid to the deviations and their relationship with the lateral wall The loca tion of obstructions and impactions were determined. There were no subjects with septal perforations in this study

Dislocation of the caudal end of the septum could be found in 17 % obstructing septum in 10 % impacting septum in 14 % and considerable deviation of the septum in 11 % of the subjects (Table 22) This exami nation supports the view that septal devia tion occurs more frequently on the left than on the right.

According to this examination no correlation could be found between the most prevalent sleeping position (table 17) and presence of impaction, obstruction or considerable de viation of the septum.

The influence of septal pathology is dis cussed in more detail in table 23 The low incidence of nasal pathology in this mate rial, as can be expected in a random sample limits the validity of statistical analysis of the correlations between symptoms and signs. Regarding obstruction and impaction some comparisons were however made with the percentages of the whole material.

Ogura's (1968) classification (page 15) of the state of obstruction in the nose has not been used in this study because the effect of separate intranasal deformities on nasal symptoms and signs has been of particular interest.

Table 23 Percentage incidence of certain symptoms and signs in the subjects with obstruction or impaction in the nose compared to the incidence in the whole material [1])

	Obstruction N = 16	Impaction N = 23	Whole material N = 162
Dyspnea {continuous, temporary, after exercise	19	14	16
Heart symptoms {coronary artery disease, pulse rate irreg	25	5	11
Sinusitis {positive irrigation, diagnosed by x ray, *suspected because of symptoms*	31	23	24
Frequency of rhinitis			
— continuous	37	23	12
— common	44	18	31
— rare	19	59	57
Sneezing			
— frequent	31	9	21
— occasional	38	55	37
Headache			
— continuous	6	9	3
— frequent	19	3	25
— seldom	50	23	31
— hardly ever	5	45	41
Epistaxis			
— unusual	25	14	22
— usual	6	9	3
Snoring			
— frequent	37	5	12
— occasional	37	55	41
Dryness of throat			
— frequent	13	14	11
— occasional	37	23	27
Mouth breathing			
— frequent	37	14	15
— occasional	19	14	8
Mid-cycle rest	0	32	7
Flat top	19	5	7
Olfactory test			
— no sensation	5	7	4
— posit. sensation	12	17	1
— identified	83	76	75
Trigeminal test			
— no sensation	6	0	1
— pungent sensation	53	41	32
— pungent sensation + identif	41	59	66

[1]) *The degree of significance is based on statistical comparisons* (Alameri *et al* 1961) *between obstruction and whole material or impaction and whole material*

Obstruction of the nose seems to produce a significant tendency to continuous rhinitis and snoring. Mid-cycle rest is typical of impaction nose and flat top deformity of the pressure curve is often connected with obstruction. The statistical significance of these findings is given in table 23. The relation of obstruction and impaction to maximal nasal ventilation and nasal breathing pressure is given in table 33.

Vestibulum. Valve-area

The density of vibrissae in the vestibulum and the structure of the valve area were examined in all subjects. In addition the mobility of the alae and the valve were estimated during nasal breathing. In five cases there was a marked deformity in the upper lateral cartilage. The results of valvular and vestibular examinations are given in table 24.

Table 24 Structural and functional evaluation of the vestibulum and valve area (per cent)

Vibrissae	
— abundant	11
— average	60
— scarce	29
Alar insufficiency	
— present	9
— absent	91
Valve area	
— obstruction	6
— normal	92
— ballooning	2
Valvular mobility	
— stiff	10
— ordinary	59
— very mobile	31

Alar or valvular mobility had no significant correlation to flow or pressure values. Only the frequency during maximal nasal ventilation tends to be higher when valve is mobile (on .05 significant level correlation). The flexibility of the valve is obviously a reason for high frequency during maximal nasal ventilation.

Cul-de-sac was wide in nine per cent and very small in 19 per cent and could be considered normal in all other cases. Wide cul-de-sac had a positive correlation (on .05 significant level) with sense of smell (trigeminal sensation and cocoa) and negative correlation (on .05 significant level) to nasal pains. According to this examination a wide cul-de-sac obviously directs the air currents more effectively to the olfactory epithelium.

Nasal airway

Obstructing polyps were found in 3 and small polyps in 0.6 per cent of the cases. 88 per cent had swollen turbinates. There were no cases of atrophy of turbinates or intranasal synechia. None of the subjects had cleft palate, choanal polyps or adenoid hypertrophy. During the examination mainly oral breathing was observed in 14 per cent of the subjects, two of the subjects had rhinolalia clausa and four had other phonetic disturbances. According to the clinical record 15 per cent of the subjects were mouth breathers.

Dependent variables

Symptoms

In table 25 the incidence is recorded of eleven symptoms considered significant for the functions of the nose or lungs or that may be caused by disturbances in their functions or structures.

Table 25 Incidence of symptoms of the upper respiratory system (per cent)

Symptoms	Frequent	Occasional	Never
Nasal pains	2	10	88
Cheek pains	2	9	89
Swallowing pains	4	1	75
Dryness of throat	11	7	82
Sneezing	23	37	4
Crusting of the nose	8	30	62
Hyposmia	6	11	83
Nose bleeding	3	22	5
Postnasal discharge	6	12	82
Snoring	12	41	47
Mouth breathing	15	8	77

Five of the symptoms were chosen by correlation analysis to represent a nasal symptom complex. The intercorrelations of these items are given in table 26.

Table 23 Percentage incidence of certain symptoms and signs in the subjects with obstruction or impaction in the nose compared to the incidence in the whole material [1])

	Obstruction N = 16	Impaction N = 23	Whole material N = 16_
Dyspnea {continuous, temporary, after exercise}	19	14	16
Heart symptoms {coronary artery disease, pulse rate irreg}	_5	5	11
Sinusitis {positive irrigation, diagnosed by x ray, suspected because of symptoms}	31	_3	4
Frequency of rhinitis			
— continuous	3	23	1
— common	44	18	31
— rare	19	59	57
Sneezing			
— frequent	31	9	1
— occasional	33	55	37
Headache			
— continuous	6	9	3
— frequent	19	23	25
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Flat top	19	5	7
Olfactory test			
— no sensation	5	7	4
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Vestibulum, Valve-area

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Table 24 Structural and functional evaluation of the vestibulum and valve area (per cent)

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— abundant	11
— average	60
— scarce	29
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— absent	91
Valve-area	
— obstruction	6
— normal	92
— ballooning	2
Valvular mobility	
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— ordinary	59
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Cul-de sac was wide in nine per cent and very small in 19 per cent and could be considered normal in all other cases. Wide cul-de sac had a positive correlation (on .05 significant level) with sense of smell (trigeminal sensation and cocoa) and negative correlation (on .05 significant level) to nasal pains. According to this examination a wide cul-de sac obviously directs the air currents more effectively to the olfactory epithelium.

Nasal airway

Obstructing polypi were found in 3 and small polypi in 0.6 per cent of the cases. 58 per cent had swollen turbinates. There were no cases of atrophy of turbinates or intranasal synechia. None of the subjects had cleft palate, choanal polypi or adenoid hypertrophy. During the examination mainly oral breathing was observed in 14 per cent of the subjects, two of the subjects had rhinolalia clausa and four had other phonetic disturbances. According to the clinical record 15 per cent of the subjects were mouth breathers.

Dependent variables

Symptoms

In table 25 the incidence is recorded of eleven symptoms considered significant for the functions of the nose or lungs or that may be caused by disturbances in their functions or structures.

Table 25 Incidence of symptoms of the upper respiratory system (per cent)

Symptoms	Frequent	Occasional	Never
Nasal pains	2	10	88
Cheek pains	2	9	89
Swallowing pains	4	21	75
Dryness of throat	11	27	62
Sneezing	21	37	42
Crusting of the nose	8	30	62
Hyposmia	6	11	83
Nose bleeding	3	22	75
Postnasal discharge	6	12	82
Snoring	12	41	47
Mouth breathing	15	8	77

Five of the symptoms were chosen by correlation analysis to represent a nasal symptom complex. The intercorrelations of these items are given in table 26.

Table 26 Intercorrelations of nasal symptoms[1])

Item	Item no	(1)	( )	(3)	(4)	(5)
Dryness of throat	(1)	—	O	O	+	+
Sneezing	( )		—	+	+*	+
Postnasal discharge	(3)			—	O	+
Snoring	(4)				—	+
Mouth breath ng	(5)					—

) N = 16_ See page 4

Table 2 Olfactory and trigeminal sensations of the subjects (per cent)

	Coffee dx	Coffee sin	Cocoa dx	Cocoa sin	Vinegar dx	Vinegar sin
No sensation	1.9	3 1	3	6 8	1_	0.6
Posit. sensation	4	16 1	29 6	3_1	30_	34 0
Substance identified	90 7	0.9	66.	61 1	68.5	65.4

Olfactory and trigeminal tests

The results of the simple screening tests of the sense of smell of the subjects are given in table 27

Tables 28 and 29 show the intercorrelations of olfactory and trigeminal items. Mucous membranes were not shrunk before testing

Table 28 Intercorrelations of olfactory items[1]) O_I = coffee O_{II} = cocoa

Item		(1)	( )	(3)	(4)
O_I right nostril	(1)	—	+	+	+
O_I left nostril	( )		—	+	+
O_{II} right nostril	(3)			—	+
O_{II} left nostril	(4)				—

) N = 162 see page 4

Table 29 Intercorrelations of trigeminal items[1]) (T = vinegar)

Item		(1)	(2)
T right nostril	(1)	—	+**
T left nostril	(2)		—

) N = 162 see page 24

Rhinomanometry

Pressure tests

The mean values and standard deviations of breathing pressures and volumes of nasal ventilation recorded by rhinomanometry are presented in tables 30 32 In pressure values no age or height correlations could be found In volume results no age correlation could be found but a positive height correlation (on 05 significant level) was noted among men.

Table 30 Mean pressures and standard deviations of nasal respiration in supine position of the subject (mm/H_2O)

	No nasal medication				After shrinkage			
	Insp rat on		Expiration		Inspiration		Expiration	
	Dx	Sin	D	S n	Dx	S n	Dx	S
Men	9 1 ±7.89	9.9 ± 03	8 7 ±6.14	10 1 ±6.57	7_ ±6.13	6.7 ±3.61	7.3 ±4 6	7_ ±4 04
Women	7 8 ±4 14	7 7 ±3.90	6.8 ±3 48	6.8 ±2.87	6.3 ±3.55	6.4 ±3 3	5 6 ± 81	5 8 ± 85
Total	8 4 ±6.09	8.6 ±5.60	7 6 ±4 90	8_ ±5.10	6 7 ±4.90	6 6 ±3 70	6 3 ±3.86	6.4 ±3 50

Table 31 Mean pressures and standard deviations of nasal respiration in side positions of the subjects (mm/H_2O)

	Right nostril up				Left nostril up			
	Inspiration		Expiration		Inspiration		Expiration	
	Dx	Sin	Dx	Sin	Dx	Sin	Dx	Sin
Men	9.4 ±8.23	7.6 ±6.25	9.0 ±5.23	7.5 ±4.54	8.3 ±5.69	7.4 ±4.38	8.4 ±4.91	7.6 ±4.70
Women	8.5 ±3.21	6.6 ±3.88	7.0 ±3.62	6.7 ±2.73	7.4 ±3.88	7.5 ±4.57	6.4 ±2.89	6.5 ±3.52
Total	8.9 ±6.72	7.0 ±4.94	7.9 ±4.49	6.5 ±3.72	7.8 ±4.76	7.5 ±4.43	7.3 ±4.02	7.0 ±4.01

Table 32 Mean pressures of nasal respiration during dilatation of the upper nostril (mm/H_2O) and standard deviations of the readings

	Right nostril up		Left nostril up	
	Inspiration	Expiration	Inspiration	Expiration
Men	5.4 ±3.78	5.6 ±3.78	4.5 ±2.88	4.8 ±3.12
Women	4.4 ±2.67	3.9 ±2.24	4.4 ±3.18	3.8 ±2.68
Total	4.8 ±3.22	4.7 ±3.12	4.4 ±3.04	4.2 ±2.86

Table 33 Relationship of septal deformity with maximal nasal ventilation (V_M) and nasal breathing pressure while subject is lying supine without nasal medication

	Obstruction		Impaction		Whole material	
N	10	8	13	10	71	91
Sex	Men	Women	Men	Women	Men	Women
V_M l/min (mean)	56 ±12.15	40 ± 7.97	60 ±22.60	43 ±10.70	66 ±19.66	42 ±15.21
Breathing pressure mm/H_2O – inspiration (mean) dx	12.6 ±13.28	12.0 ± 7.87	8.6 ± 3.18	7.0 ± 1.56	9.1 ± 7.89	7.8 ±4.14
– inspiration (mean) sin	15.5 ±14.94	11.5 ± 8.71	9.5 ± 3.96	6.6 ± 2.15	9.8 ± 7.05	7.7 ± 3.90
– expiration (mean) dx	9.9 ± 7.45	9.5 ± 4.23	9.2 ± 4.25	6.2 ± 1.34	8.7 ± 6.14	6.8 ± 3.48
– expiration (mean) sin	13.2 ±13.45	8.0 ± 3.46	10.2 ± 4.48	5.8 ± 2.27	10.1 ± 6.57	6.8 ± 2.87

No significant differences could be found when results of obstruction or impaction groups (table 33) were compared to those of whole material.

Pressure readings are a little smaller for women. There is no remarkable difference between left and right side readings. When examining the differences of the mean pressures (only results for all the subjects included) *according* to the tables above, a certain regularity can be seen between different groups

N medication	>	after shrinkage	1.3	2.0	mm/H_2O
Upper nostril	>	after shrinkage	0.8	2.3	
Upper nostril	>	lower nostril	0.5	1.1	
Upper nostril	>	dilated nostril	2.8	4.1	
Inspiration	>	expiration	0.1	1.0	

Table 26 Intercorrelations of nasal symptoms[1])

Item	Item no	(1)	(2)	(3)	(4)	(5)
Dryness of throat	(1)	—	O	O	+ *	+
Sneezing	(2)		—	+	+	+
Postnasal discharge	(3)			—	O	+ **
Snoring	(4)				—	+
Mouth breathing	(5)					—

[1]) N = 162 See page 24

Table 27 Olfactory and trigeminal sensations of the subjects (per cent)

	Coffee dx	Coffee sin	Cocoa dx	Cocoa sin	Vinegar dx	Vinegar sin
No sensation	1.9	3 1	3 7	6.8	1.2	0 6
Post. sensation	7 4	16 1	29 6	32.1	30.2	34 0
Substance identified	90 7	70.9	66 7	61 1	68.5	65 4

Olfactory and trigeminal tests

The results of the simple screening tests of the sense of smell of the subjects are given in table 27

Tables 28 and 29 show the intercorrelations of olfactory and trigeminal items Mucous membranes were not shrunk before testing

Table 28 Intercorrelations of olfactory items[1]) O_I = coffee O_{II} = cocoa

Item		(1)	(2)	(3)	(4)
O_I right nostril	(1)	—	+	+	+
O_I left nostril	(2)		—	+	+
O_{II} right nostril	(3)			—	+
O_{II} left nostril	(4)				—

[1]) N = 162 see page 24

Table 29 Intercorrelations of trige... items[1]) (T = vinegar)

Item		(1)
T right nostril	(1)	—
T left nostril	(2)	

[1]) N = 162 see page 24

Rhinomanometry

Pressure tests

The mean values and standard deviatio... breathing pressures and volumes of ... *ventilation recorded by rhinomanometr...* presented in tables 30 32 In pressure... ues no age or height correlations cou... found In volume results no age correl... could be found but a positive height c... lation (on 05 significant level) was ... among men.

Table 30 Mean pressures and standard deviations of nasal respiration in sup... position of the subject (mm/H_2O)

	No nasal medication				After shrinking			
	Inspiration		Expiration		Inspiration		Expiration	
	Dx	Sin	Dx	Sin	Dx	Sin	Dx	Sin
Men	9 1 ± .89	9 9 ±7.05	8 7 ±6 14	10 1 ±6.57	7.2 ±6.18	6 7 ±3 61	7.3 ±4 76	7 2 ±4 04
Women	7.8 ±4 14	7 7 ±3 90	6 8 ±3 48	6 8 ±2.87	6 3 ±3.58	6 4 ±3 78	5 6 ±2.81	5 8 ±2 85
Total	8 4 ±6 09	8 6 ±5.60	7 6 ±4.00	8.2 ±5 10	6 7 ±4.90	6.6 ±3 70	6 3 ±3 86	6.4 ±3 50

Table 36 gives 50 60 and 80 per cent limits of maximal nasal ventilation through both nostrils.

Table 36 50 60 and 80 per cent limits of the volume of maximal nasal ventilation (l/min) subject lying supine

	50 %	60 %	80 %
Men	52 9—81.9	48 9—85.5	37.2—92 0
Women	35 9—52.4	31.2—54.5	23 4—59 0

Vitalogram

In table 37 the vitalogram results are given with nomograms for each sex separately

Table 37 Vitalogram and nomogram results of the subjects[1])

	FEV 1	VC_N	VC	MVV_N	MVV
Men	3.51	4 86	4 64	150 1	150 0
Women	2.53	3.31	3.33	107.5	100.7
Total	2 96	3 90	3 91	126 5	122.3

[1]) FEV = volume of forced expiration, VC = vital capacity MVV = maximal ventilatory volume, VC_N = vital capacity according to nomogram MVV_N = maximal ventilatory volume according to nomogram

Tension test

The results of tension test are given in table 38

Table 38 Results of tension test

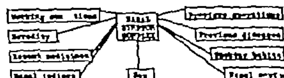
Result	Per cent
Positive	5
Slightly positiv	20
Negative	75

Correlations of nasal Symptoms and Signs

Frame of reference of symptom complex

Figure 5 shows frame of reference which presents the way of handling the results in correlation study Factors that are suggested to have some effect on nasal symptoms are included.

Figure 5



Correlations of symptom complex

The correlations of the symptom complex were examined according to the frame of reference. Only those with significant correlations are listed in table 39 A few more correlations of symptom complex are presented in table 45 (Intercorrelations of dependent variables)

Table 39 Correlations of symptom complex

	Total[*])	Male[*])	Female[*])
Working conditions			
— outdoor work	+	O	O
Previous operations			
— tonsillectomy	—	O	O
Heredity			
— asthma	+	O	O
— heart diseases	+	+	O
Previous diseases			
— rhinitis chr	+	+	+
— coronary artery disease	+	+	+
— allergy	O	O	+
— head injury	+	+	O
Smoking habits			
— duration	+	+	O
— amount	+	+	O
Nasal indices			
— salience	+	O	+
Nasal septum			
— septal deviation	+	+	+

*) N = 91 see page 24
*) N = 71 see page 24
*) N = 162 see page 24

It must be taken into consideration that upper nostril lower nostril and dilated nostril values are also taken after shrinkage of mucous membranes In side positions the congestion of turbinates has no influence on the results. The differences between the upper and lower nostrils are caused by the movements of the valve.

Co-operation with the subjects was good with three exceptions. Because of a great number of irregularities in breathing pressures one curve could not be interpreted In ten cases minor irregularities occured.

When examining the shape of rhinograms obvious flat top deformity could be seen in twelve cases. Mid cycle rest was also found in twelve cases.

Flow tests

Frequency and volume readings of flow measuring are given separately for men and women in table 34 In volume results no age correlation could be found but a positive height correlation (on 0.5 significant level) was noted among men Breathing frequencies at rest, after exercise, and during maximal nasal ventilation were about the same in both sexes. Although the breathing frequencies were nearly equal at rest and after standardized exercise, the volume of breathing was almost doubled by exercise. No significant differences could be found in volumes at rest and after exercise between different sexes, but the mean volume of maximal nasal ventilation was considerably bigger among men.

Determination of limits of normal pressure and flow values

In table 35 are given 50 60 and 80 per cent limits for pressure and flow readings obtained by rhinomanometry The mean values of 4 5 successive breaths are included, the subject is lying supine.

Table 34 Mean frequencies (resp./min) and volumes (l/min) of the nasal ventilation during flow test and standard deviations of the readings[1])

	F_R	F_E	F_M	V_R	V_E	V_M
Men	13 1	15 0	41.6	14 4	[illegible]	63.5
	± 3 61	± 3.25	±21.96	± 3 13	± [illegible]5	±19.66
Women	1[illegible]3	1[illegible]	36 9	11.5	[illegible]0 3	4[illegible]
	± 4.57	± 4.36	±15.41	± 4.33	± 6.1	±1[illegible]
Total	16.3	16[illegible]	33.9	1[illegible]	[illegible]5	5[illegible]5
	± 4.30	± 4 06	±1[illegible].63	± 3 0	± [illegible]0	±16.43

[1]) F = frequency V = volume R = at rest, E = after exercise M = maximal

Table 35 50 60 and 80 per cent limits for the pressures of nasal breathing (mm/ H_2O) subject lying supine

Normedication		50 % dx	50 % sin	60 % dx	60 % sin	80 % d	80 % sin
Men	insp.	6–1[illegible] 3	3 4–13 6	[illegible]3–13 1	4–14 0	4 3–14 3	4 5–15 [illegible]
	exp.	5 9–12.0	[illegible]–13 1	5 –1[illegible]3	3–13.	3 4–13 3	3 3–14 9
Women	insp	6.4–10.9	6 5–10 6	6.2–11 1	5 3–10.9	3.5–1[illegible]	3 3–11 9
	exp.	4 – 9 5	5 – 8 5	4.5–10 1	4 9– 9	[illegible] –10 4	[illegible]–10 0
After shrink.							
Men	insp.	5 4– 9.9	5 4– 9 5	5 –10 5	4 4– 9	[illegible]5–11[illegible]	[illegible]–10 5
	exp.	3.3–10.0	5 6–10 0	4 5–10 3	4.9–10 1	[illegible]9–11.5	3 4–11
Women	insp.	4 – 8 6	5[illegible]– 9 0	4.5– 9[illegible]	4.2– 9 1	[illegible]– 8 9	5–10 1
	exp.	4 1–[illegible]	4.5– 8 0	3 – [illegible]9	3.9– 8.1	3– 8 8	[illegible]– 9 1

Table 36 gives 50, 60 and 80 per cent limits for maximal nasal ventilation through both nostrils.

Table 36 50 60 and 80 per cent limits for the volume of maximal nasal ventilation (l/min) subject lying supine

	50 %	60 %	80 %
Men	52.9—41.8	45.9—83.5	57.2—92.0
Women	33.9—52.4	31.2—54.5	23.4—59.0

Vitalogram

In table 37 the vitalogram results are given with nomograms for each sex separately

Table 37 Vitalogram and nomogram results of the subjects*)

	FEV n	VC_N	VC	MVV_N	MVV
Men	3.31	4.86	4.64	150.1	150.0
Women	2.32	3.31	3.35	107.2	100.7
Total	2.86	3.99	3.91	140.3	122.8

*) FEV = volume of forced expiration, VC = vital capacity MVV = maximal ventilatory volume, VC_N = vital capacity according to nomogram, MVV_N = maximal ventilatory volume according to nomogram

Tension test

The results of tension test are given in table 38

Table 38 Results of tension test

Result	Per cent
Positive	5
Slightly positive	20
Negative	75

Correlations of nasal Symptoms and Signs

Frame of reference of symptom complex

Figure 3 shows frame of reference which presents the way of handling the results in correlation study Factors that are suggested to have some effect on nasal symptoms are included.

Figure 3



Correlations of symptom complex

The correlations of the symptom complex were examined according to the frame of reference. Only those with significant correlations are listed in table 39 A few more correlations of symptom complex are presented in table 45 (Intercorrelations of dependent variables)

Table 39 Correlations of symptom complex

	Total*)	Male*)	Female*)
Working conditions			
— outdoor work	+	o	o
Previous operations			
— tonsillectomy	—	o	o
Heredity			
— asthma	+	o	o
— heart diseases	+	+	o
Previous diseases			
— rhinitis chr	+	+	+
— coronary artery disease	+	+	+
— allergy	o	o	+
— head injury	+	+	o
Smoking habits			
— duration	+	+	o
— amount	+	+	o
Nasal indices			
— valence	+	o	+
Nasal septum			
— septal deviation	+	+	+

*) N = 91 see page 24
*) N = 71 see page 24
*) N = 162 see page 24

Frame of reference of nasal sign complex

In the frame of reference (Fig 4) are inclu ded factors that are suggested to have some effect on nasal signs Nasal sign complex is composed of the results of alfactory trige minal rhinomanometric, and tension tests

Figure 4



Correlations of olfactory and trigeminal complex

Combined olfactory and trigeminal variables were used to study the correlations of ol faction. The significant correlations are given in table 40

T a b l e 4 0 Correlations of olfactory and trigeminal complexs

	Olfactory[1])	Trigeminal)
Working conditions		
— outdoor work	+	+
— inconveniences at work	+	+
Previous operations		
— tonsillectomy	—	O
Previous diseases		
— rhin tis chr	+	+
— head injury	O	+
Smoking habits		
— duration	+	+
— amount	+	+
Nasal indices		
— tip index	+	O
Nasal septum		
— septal deviation	+	O
Age	—	O

) N = 162 see page 24

Correlations of pressure complex

When nasal breathing pressure was exam ined according to the frame of reference of the nasal sings only a few significant correlations were found They are given in table 41

T a b l e 4 1 Correlations of nasal breathing pressure

	No medication)	After shrinkage[2])
Previous diseases		
— sinusitis	+	O
— allergy	O	—
Recent medicines		
— antibiotics	+	O

) N = 162 see page 24

Correlations of flow complex

The minute volume of air passing through both nostrils during maximal nasal ventila tion was used as a basis for flow complex in correlation study

The significant correlations are given in table 42

T a b l e 4 2 Correlations of maximal nasal ventilatory volume

	Total)	Male[2])	Female[3])
Working conditions			
— outdoor work			
inconveniences at work	—	—	O
Heredity			
— asthma	O	O	+
Previous diseases			
— rhinitis chr	—	—	O
— headache	—	—	O
— allergy	O	—	O
Recent medicines			
— antibiotics	—	—	O
Smoking habits			
— duration	O	—	O
— amount	O	—	O

) N = 162 see page 4
[2]) N = 71 see page 24
[3]) N = 91 see page 4

Significant correlations were found to exist between breathing pressure of nasal venti lation and frequencies and volumes during flow-measurings. These correlations are given in table 43

Table 43 Correlations of nasal breathing pressures with frequencies and volumes during flow-measuring[1])

	Breathing pressure
Frequency at rest	O
Frequency after exercise	O
Frequency maximal	+
Volume at rest	+
Volume after exercise	+
Volume maximal	O

[1]) N = 162 see page 24

Correlations of tension test

Tension test correlated significantly only to the structural properties of the nose when examined relationships between tension test and background variables. These correlations are presented in table 44. Correlations between tension test and other dependent variables are given in table 45.

Table 44 Correlations of tension test

	Male[1])	Female[2])
Nasal indices		
— salience index	—	O
— tip index	O	—

[1]) N = 71 see page 24
[2]) N = 91 see page 24

Intercorrelations of dependent variables

The intercorrelations of the dependent variables used in this study are given in table 45

Table 45 Intercorrelations of dependent variables[1])

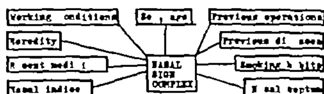
Item	Item no	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Symptom complex	(1)	—	+	+	O	—	O	—	O
Olfactory complex	(2)		—	+	O	O	O	O	O
Trigeminal complex	(3)			—	O	O	—	O	O
P cator complex	(4)				—	O	O	O	O
Flow complex	(5)					—	O	+	+
Tension test	(6)						—	O	+
Vitalogram MVV	(7)							—	+
Vitalogram VC	(8)								—

MVV = maximal ventilatory volume
VC = vital capacity
[1]) N = 162 see page 24

Frame of reference of nasal sign complex

In the frame of reference (Fig 4) are included factors that are suggested to have some effect on nasal signs. Nasal sign complex is composed of the results of alfactory trigeminal rhinomanometric, and tension tests.

Figure 4



Correlations of olfactory and trigeminal complex

Combined olfactory and trigeminal variables were used to study the correlations of olfaction. The significant correlations are given in table 40

Table 40 Correlations of olfactory and trigeminal complexs

	Olfactory[1])	Trigeminal)
Working conditions		
— outdoor work	+	+
— inconveniences at work	+	+
Previous operations		
— tonsillectomy	—	O
Prev ous diseases		
— rhin tis chr	+	+
— head injury	O	+
Smoking hab ts		
— duration	+	+
— amount	+	+
Nasal indices		
— tip index	+	O
Nasal septum		
— septal deviation	+	O
Age	—	O

) N = 162 see page 24

Correlations of pressure complex

When nasal breathing pressure was examined according to the frame of reference of the nasal sings only a few significant correlations were found They are given in table 41

Table 41 Correlations of nasal breathing pressure

	No medication)	After shrinkage)
Previous diseases		
— sinusitis	+	O
— allergy	O	—
Recent medicines		
— antibiotics	+	O

) N = 162 see page 24

Correlations of flow complex

The minute volume of air passing through both nostrils during maximal nasal ventilation was used as a basis for flow complex in correlation study

The significant correlations are given in table 42

Table 42 Correlations of maximal nasal ventilatory volume

	Total)	Male[2])	Female[3])
Working cond tions			
— outdoor work			
inconveniences at work	—	—	O
Heredity			
— asthma	O	O	+
Previous diseases			
— rhi itis chr	—	—	O
— headache	—	—	O
— allergy	O	—	O
Recent medicines			
— antibiotics	—	—	O
Smoking habits			
— duration	O	—	O
— amount	O	—	O

) N = 162 see page 24
[2]) N = 71 see page 24
[3]) N = 91 see page 24

Significant correlations were found to exist between breathing pressure of nasal ventilation and frequencies and volumes during flow measurings. These correlations are given in table 43.

Table 43 Correlations of nasal breathing pressures with frequencies and volumes during flow-measuring¹)

	Breathing pressure
Frequency at rest	O
Frequency after exercise	O
Frequency maximal	+
Volume at rest	+
Volume after exercise	+
Volume maximal	O

¹) N = 162 see page 24

Correlations of tension test

Tension test correlated significantly only to the structural properties of the nose when examined relationships between tension test and background variables. These correlations are presented in table 44. Correlations between tension test and other dependent variables are given in table 45.

Table 44 Correlations of tension test

	Male¹)	Female²)
Nasal indices		
— salience index	—	O
— tip index	O	—

¹) N = 71 see page 24
²) N = 91 see page 24

Intercorrelations of dependent variables

The intercorrelations of the dependent variables used in this study are given in table 45.

Table 45 Intercorrelations of dependent variables¹)

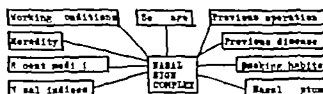
Item	Item no	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Symptom complex	(1)	—	+	+	O	—	O	—	O
Olfactory complex	(2)		—	+	O	O	O	O	O
Trigeminal complex	(3)			—	O	O	—	O	O
Pressure complex	(4)				—	O	O	O	O
Flow complex	(5)					—	O	+	+
Tension test	(6)						—	O	+
Vitalogram MVV	(7)							—	+
Vitalogram VC	(8)								—

MVV = maximal ventilatory volume
VC = vital capacity
¹) N = 162 see page 24

Frame of reference of nasal sign complex

In the frame of reference (Fig 4) are inclu ded factors that are suggested to have some effect on nasal signs Nasal sign complex is composed of the results of alfactory trige minal rhinomanometric, and tension tests

Figure 4



Correlations of olfactory and trigeminal complex

Combined olfactory and trigeminal variables were used to study the correlations of ol faction. The significant correlations are given in table 40

Table 40 Correlations of olfactory and trigeminal complexs

	Olfactory)	Trigeminal)
Working conditions		
— outdoor work	+	+
— inconveniences at work	+	+
Previous operations		
— tonsillectomy	—	O
Previous diseases		
— rhinitis chr	+	+
— head injury	O	+
Smoking habits		
— duration	+	+
— amount	+	+
Nasal indices		
— tip index	+	O
Nasal septum		
— septal deviation	+	O
Age	—	O

) N = 162 see page 24

Correlations of pressure complex

When nasal breathing pressure was exam ined according to the frame of reference of the nasal sings, only a few significant correlations were found They are given in table 41

Table 41 Correlations of nasal breathing pressure

	No medication)	After shrinkage)
Previous diseases		
— sinusitis	+	O
— allergy	O	—
Recent medicines		
— antibiotics	+	O

) N = 162 see page 24

Correlations of flow complex

The minute volume of air passing through both nostrils during maximal nasal ventila tion was used as a basis for flow complex in correlation study

The significant correlations are given in table 42

Table 42 Correlations of maximal nasal ventilatory volume

	Total)	Male[*])	Female[*])
Working conditions			
— outdoor work			
inconveniences at work	—	—	O
Heredity			
— asthma	O	O	+
Previous diseases			
— rhinitis chr	—	—	O
— headache	—	—	O
— allergy	O	—	O
Recent medicines			
— antibiotics	—	—	O
Smoking habits			
— duration	O	—	O
— amount	O	—	O

) N = 162 see page 24
*) N = 71 see page 24
*) N = 91 see page 24

DISCUSSION

The relation of nasal structure to its function and the role of the nose for the whole organism has been emphatically discussed in a number of papers and lectures by the group of nasal surgeons of the American Rhinologic Society (Williams, 1956 Cottle et al, 1958 Ogura, 1970 Hinderer 1971) and the European Rhinologic Society (Stoksted, 1953 Drettner 1970 Kortekangas, 1972). This study has been stimulated by the opinions given there and an attempt to estimate the prevalence of nasal disorders and nasal symptoms among the adult population in general has been incorporated. The questions relevant to this study are discussed in detail below

1 *Equal interval* sampling from the official register of the town of Kotka (only inhabitants from 25 to 50 years accepted) has given a representative sample of the inhabitants of the city This has been proved by the following facts different social groups were equally well represented, the working conditions of the subjects corresponded surprisingly well to those obtained by Saari (197*) and Lehto et al (197) the relation of the male and female subjects of this study was equal with the relation in the whole city Also the vitalogram examination (table 34) confirms that the material is unselected as far as pulmonary function is concerned and the same applies obviously also to other functional aspects, for the values of vital capacity and maximal pulmonary minute volume corresponded astonishingly well to the results of the nomogram

It can be considered a good result that over 80 per cent of the randomly selected subjects attended the examination. One third of those who did not attend (19 per cent of the whole sample) had an acceptable reason for their absence. Material selected in this way cannot be considered to have any special features regarding the nose. This is strongly supported by the fact that there were no cases of previous septum or pyramid operation.

2 The percentages of certain clinical notes in this study can be used as a basis for determining the incidence of nasal disorders among the adult population in general. As a sign of disturbed nasal function mouth breathing was seen in 14 per cent of all the subjects. Structural disproportions of the nose can produce a positive reaction to the tension test (25 per cent in this study) It can be assumed that changes in the skin (10 per cent) in the mucose membranes (31 per cent) and increases in the amount of nasal secretion (38 per cent) are connected to certain pathological states of the nose. In the course of this study a large number of structural deformities of the nose were revealed deformity of the external pyramid (18 per cent) deformity of the tip (11 per cent) deformity of the columella (30 per cent) deformity of the nostrils (18 per cent) and deformity (impaction, obstruction or considerable deviation) of the septum (26 per cent) Most of these findings can be considered to be independent signs of the pathological state of the nose. Thus it can be concluded that the mean of the percentages mentioned above (22 per cent) roughly corresponds also to the incidence of functional disorders in the noses of the test subjects. From this statement can further

pine position of test subjects was selected to make it easy to find equal condition for every subject. This position also made it possible to examine the effect of the valve on the breathing pressure when the head of the subject was alternately turned so that right nostril or left nostril was up In side positions the effect of the congestion was eliminated by medication.

It seems to be difficult to check whether the test subject is breathing normally Rather often forced breathing started as soon as the nozzle was in place. In these cases the test subject was asked to relax and the test was repeated. The pressures and minute volumes, however varied a lot from person to person, often without any obvious reason. Therefore maximum nasal ventilation was selected from the various possible test methods. This study seemed to show a great difference in the incidence of significant correlations of maximal nasal ventilation between men and women. This can be explained by the fact that it was most important for men to gain good functional results, and because of that they got results which were obviously very near to their real maximum. The correlations for male subjects are therefore more reliable than those for female subjects.

Because the material is relatively small and comprised of normal subjects, it was considered to be justified to use quartile division (25 % — 50 % — 25 %) in examining nasal functions. If the corresponding variables had been based on an assumed degree of nasal disorders (e.g 10 % — 80 % — 10 %) more correlations would certainly have been obtained, but occasional extremes of value would probably have become too significant.

5 In this study the subjects were lying supine during the pressure measurings. As stated by Rundcrantz (1964) changing the posture of the subject from sitting to supine position did not cause any significant increase in air flow resistance in normal cases. Among allergic patients, however the resistance increased markedly within a few minutes. The supine position is firm and stable and the subjects are well relaxed, which makes it easier to achieve standardized conditions. Relaxation probably also makes the subject breathe quietly without hyperventilation. Thus the results of supine measurings can be compared with the results obtained by Cottle (1965) and Kortekangas (1972) in sitting subjects.

When trying to construct the norms for breathing pressures and flow readings, the limiting values of the middlemost 50 60 and 80 per cent were examined (tables 35 and 36) As far as the pressure values were concerned, the limits for 80 per cent seemed to represent the limits for normal function, because when moving from the limits of 60 per cent to those of 80 per cent, the deviation of results was relatively slightly bigger than when moving from the limits of 50 per cent to those of 60 per cent, in other words occasional extremes of value begin to have some effect on the results. In flow values the same effect can be seen so perhaps limiting values of 80 per cent give the best limits for what can be described as normal. Norms for the pressure of nasal respiration are thus (mm/H_2O)

Inspiration	men	women
right nostril	4.5—14.3	3.5—12
left nostril	4.5—15.5	3.5—11.9
Expiration		
right nostril	3.4—13.3	2.7—10.4
left nostril	3.8—14.8	2.5—10.6

Norms for maximal nasal ventilation (l/min) are for men 37.2—99.0 and for women 23.4—59.0

If the results of maximal nasal ventilation are compared with vitalogram results, it can be seen that the mean volume of maximal nasal ventilation for men was 44

be concluded that about 20 per cent of the results obtained by rhinomanometry are in the range of extreme values that can be considered abnormal

3 According to the clinical nasal index nearly all the noses in this study can unquestionably be classified to the leptorrhinians (table 20) Only 7 4 per cent range to any other group Earlier studies using *cephalometric indices suggest that in Fin*land 47—96 per cent of the noses of the native population are of the leptorrhinian type (Roschier 1931 Arho 1934 Pesonen, 1935 and 1937 Lofgren 1937 Mustakallio and Telkka 1951 and Telkka 1953)

On the other hand only 43 per cent according to the tip index and 44 per cent according to the salience indices belonged to the leptorrhinians. Can this be explained by some Special characteristic of the noses examined? During the last decades the mean height of the population has increased, as stated also in this study No correlation could be found between height and clinical nasal index or tip index. On the other hand a high significant positive correlation was found between height and salience indices This is apparently explained by the increase in the prominence of the bony pyramid among tall people. According to this study the profile of the nose was only in eight per cent convex, and in the studies by Mustakallio and Telkka (1951) and Arho (1934) the profile of the Finnish nose was convex *in 4 9—31 6 per cent. Although the bony* pyramid of the Finnish nose is exceptionally low the high salience readings can be explained by the facts that the base of the nose is rather small (nostrils are elliptical or narrow in 85 per cent of the subjects) and rounded or quadratic (tip index values are relatively high)

With only one exception all noses which according to the tip index belonged to the leptorrhinians belonged to this group also according to the clinical nasal index

To conclude, the average nose according to this study belongs to the leptorrhinians, its profile is concave or straight, the tip index and salience indices are *relatively high* owing to the small rounded or quadratic base of the nose. The nostrils are mainly elliptical

4 The reliability of most testing methods in this study is based on subjective conception (evaluation of clinical findings, tension test) and accuracy (measuring indices, photography) of the author and making the *test subject spontaneous and co-operative* (olfactory trigeminal vitalogram and rhi*nomanometric testings) Co-operation was* found to be good in 98 per cent during rhinomanometric examinations. As a result of careful planning of the test methods no changes had to be made in the order or manner of performing the tests.

Indices obtained by photography were regularly smaller than those obtained from nasal measurings (table 18) To increase the reliability of the indices measured from *slides* the points of measuring *should* be marked on the skin before photography Color slides proved to be of special importance when notes about the structure or appearance of the nose were checked afterwards

The amount of positive olfactory and trigeminal sensations was probably *diminished* because the mucous membranes were not shrunk before the testing of the acuity of *the smell Thus the results obtained do not* correspond only to the state of the olfactory epithelium and its pathways but also to the state of the congestive tissues inside the nose. The test substances were familiar to everybody and they were also quite strong stimulants and could easily be recognized *if the condition of the nose was normal*

The reliability of vitalogram tests was confirmed by the fact that the results obtained by *it corresponded well to the nomograms.* During rhinomanometric examinations su

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5. In this study the subjects were lying supine during the pressure measurings. As stated by Runderantz (1964) changing the posture of the subject from sitting to supine position did not cause any significant increase in air flow resistance in normal cases. Among allergic patients however the resistance increased markedly within a few minutes. The supine position is firm and stable and the subjects are well relaxed, which makes it easier to achieve standardized conditions. Relaxation probably also makes the subject breathe quietly without hyperventilation. Thus the results of supine measurings can be compared with the results obtained by Cottle (1963) and Kortekangas (1972) in sitting subjects.

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If the results of maximal nasal ventilation are compared with vitalogram results, *it* can be seen that *the* mean volume of maximal nasal *ventilation* for men was 44

per cent and for women 42 per cent of the mean volume of maximal pulmonary ventilation.

6 Correlations of nasal symptoms and signs are discussed here according to the frames of reference. Symptom complex was formed of 5 items which were selected on the basis of intercorrelations from 11 nasal symptoms Olfactory trigeminal pressure, and flow complexes were also formed using available items to represent nasal signs in correlation studies. Symptom complex revealed as expected significant positive correlations as to chronic rhinitis deviation of the septum prominent nose, and allergy (table 39) Surprisingly enough a high positive significance could be found between symptom complex and coronary artery disease There were some environmental circumstances which significantly coincided with nasal symptoms. According to this study smoking outdoor work, severe head injury and heredity (asthma and heart diseases among close relatives) had significant positive correlations to the symptom complex A previous tonsillectomy on the other hand had a significant negative correlation to nasal symptoms There was no evidence in this study of oral contraceptives having any effect on the occurence of nasal symptoms

It was possible in this study to trace a significant degree of coincidence between smoking chronic rhinitis working conditions and the sense of smell (table 40) There was a significant correlation between olfactory acuity and the deviation of the septum This is explained by the fact that septum deviation in many cases obviously directs air currents away from the olfactory epithelium Also the structure of the base of the nose had some effect on the direction of air currents because the tip index had a significant correlation with olfactory acuity i.e. the increase in the tip index values made the olfactory acuity better

Leigh (1943) Sumner (1964) and Caruso *et al* (1969) stated that the sense of smell is weakened by earlier head injury According to this study a severe head injury had a significant correlation only with trigeminal sensitivity According to Strauss (1930) the sense of smell was weakened when the subject was getting older In this study a significant lowering in olfactory acuity was found with advancing age, but no significant coincidence was found with trigeminal acuity According to v Dishoek (1963) allergy causes hyposmia this result was, however not confirmed in this study

The fact that no significant correlations could be found in this study between nasal breathing pressures and deviations or deformities of the septum can be explained by rather big variations in the normal values of breathing pressures. As stated by Cottle (1968) marked increase in breathing pressure practically always means a nasal obstruction In this study allergy which obviously means swollen turbinates, coincided significantly with breathing pressure. Breathing pressure had also significant correlation with the frequency of maximal nasal ventilation In other words obstruction of the nose causes a high breathing frequency during maximal nasal ventilation. An obstructed nose obviously leads to forced nasal breathing because nasal breathing pressure correlated significantly with the volume of nasal ventilation at rest and after exercise.

No significant coincidence could be found in this study between weight at birth and septum deformities Also Jeppesen and Winfeld (1972) could not find any relationship between weight at birth and the number of septal dislocations According to this study (table 44) tension nose corralated significantly among men with the salience index and among women with the tip index. Hinderer (1971) also found relationship between structural properties and tension of the nose

According to this study only chronic rhinitis, snoring and trigeminal sensitivity correlated significantly with septal obstruction. The subjects with septal obstruction also had considerably more frequently heart symptoms, mouth breathing sinusitis, and *sneezing* but the differences did not reach the level of significance.

In rhinogram the mid-cycle rest deformity correlated significantly with the impaction of the septum. In cases with impaction continuous headache was a common finding whereas the flat top was found relatively seldom. The incidence of both mid-cycle rest and flat top on the pressure curves in relation to obstruction or impaction of the septum was the opposite of what was found by Cottle (1968). Obstruction seems to decrease maximal nasal ventilation and increase the pressure of normal breathing. No significant relationship could however be found in this examination, probably because of the small number of cases investigated (table 25).

On examination of the intercorrelations of *dependent variables (table 45)* a significant relationship was found between nasal symptoms and olfactory and trigeminal sensitivity. The symptom complex correlated significantly with maximal nasal ventilation and maximal minute volume of the lungs. There was a correlation of high significance between olfactory and trigeminal sensitivity. The tension of the nose had a significant relationship with trigeminal acuity. The volume of maximal nasal ventilation had a positive significant correlation with the maximal minute volume of the lungs and the vital capacity of the lungs. The minute volume and the vital capacity of the lungs had a intercorrelation of high significance.

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SUMMARY

Two hundred inhabitants of Kotka, whose names had been obtained by equal interval sampling were invited to come for an examination of the nose and upper respiratory system. Results of nasal signs investigated and answers to a number of inquiries regarding nasal and related symptoms, environmental circumstances e.t.c. were available for 162 persons. The representativeness of this group was proved by the facts that different social groups, both sexes and variations in working conditions were represented according to the expectations and that the results obtained by vitalogram corresponded exactly to the nomogram.

As the subjects were picked out by an equal interval sampling it was to be expected that they would mainly be people in a normal state of health. Structural changes were found in different parts of their noses, which on average could be considered abnormal in 20 per cent.

Anthropologically 92.6 per cent of the subjects belonged to the leptorrhinians according to the clinical nasal index. The bases of the noses examined were obviously different from the typical leptorrhinian nose, because according to the tip index only 44 per cent range to this group. Only 6 per cent of the noses examined had convex profiles. All the subjects who had a convex profile of the nose belonged to the leptorrhinians according to the clinical nasal index. With only one exception all noses which according to the tip index belonged to the leptorrhinians, belonged to this group also according to the clinical nasal index.

Quartile division of the functional results was used for correlation studies to avoid extra correlations by extremes of value. Cooperation was good with the subjects in 98 per cent during rhinomanometric examinations.

The norms for the rhinomanometric results were based on the incidence of nasal disorders (about 20 per cent) and on the fact that the limits for 80 per cent seemed to represent the point after which occasional extremes of value began to have some effect on the results. Limits for normal breathing pressures changed among men from 3.4 to 15.5 mm/H_2O and among women from 2.5 to 12.2 mm/H_2O. The mean of the maximal nasal ventilation was for men 44 per cent and for women 42 per cent of the mean volume of the maximal pulmonary ventilation. The limits for normal maximal nasal ventilation were for men from 37.2 to 92.0 and for women from 25.4 to 59.0 l/min.

Special attention was paid to studying correlations between nasal symptoms and signs and numerous environmental circumstances called background variables. Based on the intercorrelations of 11 nasal symptoms five of these (dryness of throat, sneezing, post nasal discharge, snoring and mouth breathing) were selected to represent all the symptoms in correlation studies as a symptom complex. Also of nasal signs were formed combined variables which respectively were called olfactory, trigeminal, pressure, and flow complexes.

The nasal symptom complex correlated significantly to a number of background variables. Significantly higher incidence of nasal symptoms occurred in subjects with chronic rhinitis, septal deviation, prominent nose, allergy, coronary artery disease,

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smoking outdoor work and severe head in jury Significantly lower incidence of nasal symptoms was found in subjects whose ton sils had been removed

Significant relationships could be found in this study between olfactory acuity and smoking chronic rhinitis outdoor work in convenience at work deviation of the sep tum tip index, and the age of the subject. There was some difference in the correla tions of trigeminal acuity which had sig nificant correlations to smoking chronic rhi nitis outdoor work inconvenience at work, and severe head injury

No significant correlations could be found between nasal breathing pressure and devia tions or deformities of the septum obviously because of rather big variations in the nor mal values of the pressure. If the pressure was raised, the volume of nasal breathing was significantly increased at rest and after exercise

Obstruction of the nose correlated signifi cantly only with chronic rhinitis snoring and trigeminal acuity in this study Im paction of the septum correlated significant ly with mid cycle deformity of the rhino gram

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SUPPLEMENT 322

Headaches with Positional Nystagmus Mechanism and Cure

BY

A. C. ARULPRAGASAM

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Headaches with Positional Nystagmus

Mechanism and Cure

BY

A C ARULPRAGASAM

From the Department of Otolaryngology
General Hospital, Colombo, Sri Lanka (Ceylon)

UPPSALA 1974

Introduction

The headaches studied here are the common troublesome and frequently recurrent headaches—sustained muscle contraction headaches While these are known to be caused by noxious pathology in the head and neck and also to occur after head injury those dealt with here are those occurring spontaneously As a cause of these Swanson (1971) suggests conceptions such as emotional tension states anxiety frustration or depression. He also says these headaches are due to contraction of skeletal muscles about the face scalp and neck and also that concurrent vasodilatation of the associated cranial arteries frequently contributes to the irritability of the involved muscles and to the headache. He says tinnitus dizziness and lacrimation occur with the headaches and that these may be produced or increased by pressure on the contracted muscles No treatment appears to be of any avail Ostfeld (1963) says that in many cases of migraine (77 out of 114 patients) a so-called 'background headache appears which he diagnosed clinically as skeletal muscle contraction headache. It is useful to state here that Schiller & Hedberg (1960) finding PN in a group they classified as anxiety and also observing that the majority of patients in this group suffered from vascular or tension (muscle contraction) headaches also wonder about the relationship of PN both to anxiety and to the headache and make the admission that they are open to criticism because they failed to give a clear-cut answer to the question whether PN in this group ("anxiety) is a psychosomatic or a somatopsychic manifestation

In this study the muscle contraction headaches have been diagnosed clinically from their vice-like or gripping nature gradual onset and increase and very frequent recurrence, differentiating them thus from the vascular headaches (Graham, 1963) which have a throbbing quality sudden onset with or without aura, and less frequent recurrence He also says that the headache in the muscle contraction type is really a constant one (with frequent exacerbations)

On the basis of a certain neuro-otological conception and a minor otological interference it has become possible to cure completely 100 consecutive cases of muscle contraction headaches and thus come to a conclusion on their mechanism of production Two new signs are here described in relation to these headaches and there is reason to believe that these are applicable to the Vascular Headaches also Light is also shed on the PN that accompanies these headaches since in this work the PN has been made to disappear in a 100 cases

Theory

Positional nystagmus (PN)

The PN seen in these cases was a brisk, sustained (right through the maintenance of the Position) non-fatigable non-paroxysmal horizontal first-degree nystagmus of the central type (Edwards 1971) Since it follows from what will be said in this article that it

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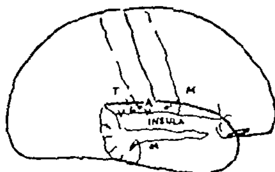


Fig 2 LCA, *T* taste area *M* scalp muscle motor *A* auditory sensory *V* vestibular projection It will become accepted that LCA extends onto the superior surface behind *A* to be contiguous with *T* The area for nausea and vomiting *N* on the anterior part of the insula, *N* temporal lobe stem

have used the electron microscope and histochemical methods to detect the presence of nerve fibres showing acetylcholinesterase (AChE) activity in the non-acoustic and acoustic labyrinth of animals. Iurato et al (*1971*) have shown efferent nerve fibres (unmyelinated) with AChE activity in the vestibular sensory areas of the chinchilla. In this species the efferent fibres appear to take a separate course from the brain stem along with the afferent fibres Terayama & Yamamoto (1971) studying the olivo-cochlear bundle in the guinea pig, found efferent endings and preterminal fibres inside the organ of Corti and state that their relationship to the myelinated and unmyelinated efferent fibres outside the organ still remains unknown It is here advanced that parasympathetic efferent nerve terminals are *to* be found in the human inner ear both non-acoustic and acoustic The *experimental* investigations in animals would appear to speak in support of this view rather than controvert it. The work of Ishii (1971) in *the rat* appears to show that these *fibres* could not have found their way into *the* inner ear along the blood vessels though he found AChE activity in the stria vascularis and spiral ligament behind the external sulcus and the author here and elsewhere makes the serious claim that the LB to the CT is an anatomical entity

Regarding these LCAs it will be postulated that they lie in the middle of the superior temporal gyrus of each side (Fig. 2) While there are many reasons for saying this those of immediate concern are that they must be in close association with the cortical vestibular projection areas on each side which Behrman & Wyke (1958) after studying all the relevant evidence conclude as extending forward from behind the primary acoustic area to lie below and lateral to the latter in the superior temporal gyrus There is also the reason that Carmichael et al (1954) have shown that a destructive lesion in the posterior part of the temporal lobe (posterior part of the superior temporal gyrus) produces a modifying influence on caloric nystagmus namely a directional preponderance i.e a directional *sensitivity* towards the affected temporal lobe Evidence will emerge in this work that this LCA lies exactly *where it is postulated to be and* that it is an effector area. The consequences that follow in the study of these headaches will be *seen to confirm this* original assumption and postulation.

Thus the conception arises here that a minor subdued enduring epileptiform activity *in say the left LCA*, produces increased discharge activity in the right LB giving a PN on the right side i.e. in the right lateral position *and minor* vertiginous *symptoms*, which *may* be called episodic *central* positional vertigo with PN A further conception arises *that* if this disturbance occurs *to a nearly equal* extent in both LCAs then *there* will occur what may be called latent *episodic* central positional vertigo *with bilateral PN (direction changing)* The subject may then not admit that he is *dizzy but may be* shown to be unsteady in Romberg's test with eyes closed *or in a Tandem Romberg* test. The possible connections and interactions between this neuronic circuit and other *parts of the* nervous system need

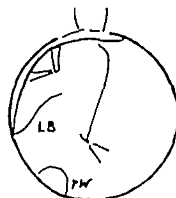


Fig 1 LB runs under the mucosa of the posterior wall below the pyramid and the stapedius tendon proximal end of CT is a guide to its location *rw* round window

is to be found in all the functional headaches and many other conditions the question may be posed whether this is not a normal phenomenon and that an effort is being made to read some significance in it. There is also an opinion expressed that nystagmus in the extreme limits of gaze is often present in normal persons in the erect position This apparently is not the view of other authorities like Nylen (1950) and Schiller & Hedberg (1960) who examine for a first-degree PN and the latter comment that it is this type of PN that is usually found Even if it is true that some nystagmic jerks are to be found on extreme deviation of the eyes in normal persons (and in the positional test this alters to a brisk sustained non-fatigable nystagmus) then it will in fact become a PN In 3 cases out of the 100 studied here there was a spontaneous nystagmus on extreme deviation of the eyes either to right or to the left In one case it was an ocular or pendular nystagmus and since the author was convinced despite the spontaneous nystagmus they exhibited that they had a PN and also unsteadiness etc they were accepted and treated with successful results In the two who had a vestibular type of spontaneous nystagmus the nystagmus also disappeared In the other 97 cases no nystagmic twitch with extreme deviation of the eyes in the erect position was seen In all of them after a certain interference with the chorda tympani (CT) nerves the PN disappeared and the headache ceased and did not recur Also it will be found that there are many situations in which this type of PN appears and disappears For instance this will be found to be so in the Vascular Headaches as has already been described in Chorda tympani neuralgia and Recurrent Parotitis (Arulpragasam 1974 and 1967)

The author (1967) studying Recurrent Parotitis and a rather rare syndrome of vertigo and salivary gland enlargement e g submandibular gland enlargement usually without a calculus came to the conclusion that there was a neuronic circuit which acted as some sort of feed-back mechanism to the labyrinth and also that if this circuit was disturbed by an epileptiform process on one side there was vertigo and a PN In this study there is a further confirmation of the existence of this neuronic circuit and convincing evidence that the disturbance is an epileptiform one and that it occurs in the cerebral cortex The essential parts of this circuit on each side is a Labyrinthine Cortical effector area (LCA) connecting by efferent fibres with the opposite side of the brain stem to a special labyrinthine nucleus which most likely is a part of the superior salivatory nucleus of the CT nerve Fibres continue from here with the other fibres of the CT nerve and just as the nerve enters the middle ear from the iter in the bone of the posterior wall (Fig 1) the labyrinthine branch (LB) is given off and courses medially under the mucosa of the posterior wall and hence cannot be seen Regarding this LB it will merely be stated that in the course of many hundred tympanotomies in the past eight years this LB has been seen on two occasions when it was abnormally and more anteriorly placed than usual The consistent and successful results of this study and the other evidence that emerges will constitute overwhelming confirmation and proof that there is a LB It would appear useful to draw attention to the findings of observers who

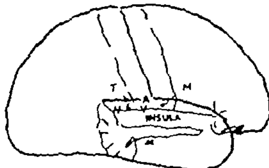


Fig. LCA. T, taste area; M, scalp muscle motor; A, auditory sensory; V, vestibular projection. It will become accepted that LCA extends onto the superior surface behind A, to be contiguous with T. The area for nausea and vomiting is on the anterior part of the fasciola. st, temporal lobe stem.

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Thus the *conception arises here* that a minor subdued enduring *epileptiform* activity in say the left LCA, produces *increased discharge* activity in the right LB giving a PN on the right side, i.e. in the right lateral position, and minor vertiginous symptoms, which may be called episodic central positional vertigo with PN. A *further* conception arises that if this disturbance occurs to a nearly equal extent in both LCAs *then there will* occur what may be called latent episodic central positional vertigo *with bilateral PN* (direction changing). The *subject* may then not admit that he is dizzy but may be shown to be unsteady in Romberg's test with eyes closed, or in a *Tandem Romberg test*. The possible connections and interactions between this neuronic circuit and other parts of the nervous system need

not be considered here and such as are necessary for the purposes of this thesis will become apparent and acceptable

Taste

The conception arose that when there is a central disturbance in the LB fibres of the CT nerve there would also be a significant delay in taste perception to chemical testing on the relevant part of the tongue This expectation has materialized to always be so *in fact Why only the taste pathways* are disturbed and not the other fibres in the nerve such as those for pain and secretomotor activity (the latter has not been studied) will become apparent from what is to follow

In this study the subject was made to *keep the tongue protruding out of his mouth* and a simultaneous and liberal application of *moist salt crystals was made to both anterior* halves of the tongue along the sides The subject was told the application could be either salt or sweet He indicated perception on each side by raising his hands off his knees both together if the perception was simultaneous or one at a time as the case may be As he took his tongue in he stated what the modality of taste was Occasionally *a patient said that it was bitter or sweet* before he perceived the salt In a normal subject in this test salt is perceived within five seconds and *simultaneously on both* sides This appears to apply even to the older subjects and to smokers Salt crystals were always used for testing since it was found that in those patients *with delayed* taste perception say to sweet was so tardy that it could be taken as no perception at all or aguesia The outside limits of what is normal could be accepted as 7 seconds and simultaneous perception One normal subject who was in a position to remonstrate with the author said after raising *both her* hands at 7 seconds that she had delayed becuase of the confusion the author had caused by saying that the application could be of salt or sweet *In the patients themselves* first of all taste perception was never simultaneous on both sides and this in itself should lead to suspicion In about *70% of cases the delay was over 20 sec* on one or both sides and at this stage the test was abandoned and recorded as over 20 sec In 23% *of cases it was over 15 sec.* In 7% of cases the perception was 12 sec or under In some of these the case may have been they were headache free at the time but in 3% of cases altogether the perception was in 3 or 4 sec and almost simul*taneous on both sides For these the explanation already advanced will not be ac*ceptable It will be seen that slight variations in the pattern of the disturbance that causes the headache and also the possibility that the cortical taste centre could be abnormally situated could be likely explanations It will also be seen that even though it was subsequently established that the in*nervation for taste was abnormal in some* cases taste perception had been delayed before their operations and returned to normal after the event This observation alone taken in conjunction with the other phenomena and observations in these patients localizes the disturbance at a cortical level

The *opinion has been expressed* that taste perception to chemical testing can be found delayed in normal individuals It will be *readily accepted that when previous studies* were done the subjects with muscle contraction headaches themselves were not excluded as subjects unsuitable for study It *will also be agreed that subjects suffering* from vascular headaches in all of whom it will be found that there is a taste delay at some time or other constitute a considerable proportion of the population In addition to this the author now knows that there are many and diverse other conditions in *which there is a taste delay* These conditions it would appear are to be categorized among those conditions which are now

called Psychogenic dizziness It will be agreed that these patients are ubiquitous and to the otologist at any rate represent a condition of uncertain aetiology In order to afford a comprehension of the author's rather unusual experience in this regard the following may be recounted About 7 years ago an adult male of 52 years complaining of what appeared to be rather minor dizziness which he wanted to be rid of was treated by avulsion of his right CT nerve His dizziness ceased and the feeble PN he exhibited in the right lateral position disappeared What is relevant here is that he had had a previous consultation with a neurologist of repute and the diagnosis had been Psychogenic dizziness This category it will be found and shown in a later communication to be so is further enlarged by patients who do not complain of dizziness but show a bilateral (direction changing) PN and what may be called neurotic or anxiety symptoms. In all these conditions if the symptoms are of a transient nature, taste perception will be found to return to normal If the disturbances are of an enduring nature such as occurring in these muscle contraction headaches taste perception can be made to return to normal as has been done even in this study in some cases and this is to be the expectation in all the cases if only the LB had been ablated without avulsing the CT as the method of treatment. This position will become acceptable from what is to follow It will be found that delay in taste perception to the test here described is always (or almost always) associated with this type of first-degree central type of PN directed away from the undermost ear It will also be found that the symptoms these patients complain of whatever they may be, have a relationship to this PN and delayed taste perception. This test for taste will certainly become useful and be found to embody an important conception perception will be found to improve as the symptoms decrease and return to normal when the latter cease Many of these patients have apparently hitherto been considered normal subjects showing delayed taste perception to chemical testing.

It appears that there is some evidence in this work that, in some cases at any rate this first-degree central type of PN associated with delayed taste perception is not a psychosomatic manifestation but a somatopsychic one and thus perhaps the ground work has been laid for the extension of the conception that some emotional disturbances may have a physical basis and that, it might be possible to manipulate this beneficially These muscle contraction headaches for example If the opinion of such authorities as Swanson (1971) is to be accepted, suffered from anxiety emotional tension and other allied manifestations and the majority of them at any rate would not agree that they had any of these features after they had been relieved of their headaches as has been done here.

Headache

With this conception regarding *vertigo* and the type of PN discussed here accepted the meeting point with the treatment of the functional headaches had to occur at some time or the other For it will be found that the vertiginous symptoms which are known to occur with all known functional headaches both muscle contraction and vascular are due to *a derangement of the* mechanism *defined here* In the rather exceptional circumstances of one of these headache patients refusing to admit to being dizzy it will be found that they have what has been *called* here latent central positional vertigo *with PN* Very exceptionally they do not exhibit PN during a headache, but the other relevant signs can be found In the vascular headaches these signs are to be found during the phase of a headache and in the muscle contraction headaches which really have a constant background of headache

these signs are to be found at any examina tion *This meeting point was more likely to* happen in the circumstances the author found himself in These circumstances were *that during the relevant years he was the* sole Otolaryngologist to what is called a Provincial Hospital in this country A few years ago such a hospital had neither Neurological nor Psychiatric services Also *there was and is no referral system func* tioning In this situation patients with head *aches sought either the author s advice or the* advice of the Ophthalmologist While no doubt many little steps and almost sub-conscious observations led to the develop-ment described here the occasion that stands out in memory was the occaion early in 1965 when a young man with a fairly severe right sided *headache* of nearly one month s duration presented himself for ex *amination He had already sought neurologi* cal ophthalmological and otolaryngological advice elsewhere The usual examinations revealed nothing an examination was made with regard to the minor vertiginous symp-toms he admitted to having When it was found *that* they were due to the mechanism discussed here he was offered a minor oto-logical procedure with a possibility of being relieved of his trouble This in his distress he did accept On the next morning his right CT nerve was avulsed in the afternoon he was transformed—according to him he had not even a vestige of a headache nor did *it recur subsequently After this all head* ache patients seeking treatment were ex amined in the manner to be described and a minor otological procedure offered and with increasing confidence a cure was also guaranteed Many accepted and the type of headaches that presented were the sponta-neously occurring muscle contraction head-aches In early 1966 it was decided to study this series presented here and follow up the cases adequately It would appear that vas *cular headaches are not very common in this* country and so it came about that it was the muscle contraction headaches that were initially studied

Composite Case History

The patients were usually young adults or adolescents with a history of recurrent and *troublesome headaches of many years* duration The headaches were either bi *lateral and diffuse or unilateral The loca* tion was usually fronto-temporal though sometimes there was an ache towards the back of the head in addition The usual pattern was that of 3 headaches a week lasting about 2–3 hours Strain and fatigue of working or travelling especially in the sun was often alleged to bring on the headache Remissions were known but never of more than 2–3 weeks Some said that the head ache was really constant In most of them dizziness accompanied the headache and was noticeable when the headache was severe In 2 or 3 the dizziness was nearly as troublesome as the headache Two said that they had no dizziness at all In nearly half the patients the headache was accompanied *by a low pitched tinnitus either in* one or both ears As an after thought enquiry was made and it was found that tinnitus reached *its maximum intensity with the headache* and ceased when the headache left Even in this early study and because it was sponta neously mentioned by them *there had been* excessive sweating in 5 patients Two had spontaneously mentioned lack of concentra-tion and defective memory among their com plaints A fair number had complained of intermittent fullness in the ears and 6 had complained of intermittent itching *Drowsi*

ness was reported by 4 patients Few patients had nausea with their headaches and fewer still actually vomited at the height of their headache and this not always so Enquiry had been made about travel and reading and some patients had complaints to make in this regard and these will be referred to in what is to follow In a few lacrimation also occurred especially during the headaches and this was provoked by reading or looking at the sun or any bright light Enquiry was not made into their emotional state since this appeared to be fraught with difficulties It was of course noticed that a few patients looked visibly anxious or depressed before their operations

Material

The 100 patients came from all walks of life They were usually young adults or adolescents The average duration of their complaints was 4 years and 10 months The longest history was 30 years and the shortest 6 months in a student who said his studies were affected by the headaches There were 39 males and 61 females The oldest patient was 72 years old and the youngest was 11 and he alleged a moderately severe head injury preceded and caused the headaches In 48 the headaches were bilateral and diffuse In 52 the headache was unilateral on one or the other side

Examination

PN

The patient was made to lie on a bed in the right lateral and left lateral positions and made to look up at the roof with extreme deviation of the eyes The presence or absence of PN was noted. The results of examination for spontaneous nystagmus has been mentioned earlier The PN was an immediate brisk, horizontal non-paroxysmal non-fatigable first-degree nystagmus, directed away from the undermost ear In 47 cases the PN was bilateral (direction changing with change of position of the head) and in 53 the PN was unilateral (direction fixed) Thus only one case was an exception to the rule that in unilateral headaches the PN was unilateral and bilateral in diffuse headaches The PN was always on the side of the headache (side of PN means the side of the lateral position in which the PN is seen this is the same side as the side of the headache) This is a very satisfactory correlation The one exception of a patient with diffuse headache with unilateral PN was asked about his headache months after the operation when this discrepancy was discovered he did not alter his story but actually he said that he had forgotten. It may be mentioned that the preliminary examination for PN was made by merely pushing the patient's head backwards and to each side in turn in the clinic chair This slap dash method is useful when many examinations for PN are made in a busy clinic In this series it was not found that the neck reflexes had modified the PN even in a single case In some cases the PN was not brisk, then perhaps subsequent examinations helped It will be found that the PN can vary in briskness from examination to examination and appears to have a correlation

these signs are to be found at any examina tion This meeting point was more likely to happen in the circumstances the author found himself in These circumstances were that during the relevant years he was the sole Otolaryngologist to what is called a Provincial Hospital in this country A few years ago such a hospital had neither Neurological nor Psychiatric services Also there was and is no referral system func tioning In this situation patients with head aches sought either the author s advice or the advice of the Ophthalmologist While no doubt many little steps and almost sub-conscious observations led to the develop-ment described here the occasion that stands out in memory was the occaion early in 1965 when a young man with a fairly severe right sided headache of nearly one month s duration presented himself for ex amination He had already sought neurologi cal ophthalmological and otolaryngological advice elsewhere The usual examinations revealed nothing an examination was made with regard to the minor vertiginous symp-toms he admitted to having When it was found that they were due to the mechanism discussed here he was offered a minor oto-logical procedure with a possibility of being relieved of his trouble This in his distress he did accept On the next morning his right CT nerve was avulsed in the afternoon he was transformed—according to him he had not even a vestige of a headache nor did it recur subsequently After this all head ache patients seeking treatment were ex amined in the manner to be described and a minor otological procedure offered and with increasing confidence, a cure was also guaranteed Many accepted and the type of headaches that presented were the sponta neously occurring muscle contraction head-aches In early 1966 it was decided to study this series presented here and follow up the cases adequately It would appear that vas cular headaches are not very common in this country and so it came about that it was the muscle contraction headaches that were initially studied

Composite Case History

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small minority It would appear that the actual incidence of unilateral trouble is about 20 to 25% In the early days when a bilateral operation was suggested patients tended not to accept, and when the persuasive after all it is to be a tiny operation in one ear was offered the patient tended to accept. Even today middle-class patients who do not know the author appear to be prejudiced against the procedure however troubled they are they apparently know enough to know that headaches cannot be cured through the ear and that an ear operation particularly a bilateral one could make them deaf The operations were usually done under local anaesthetic and moderate sedation. A reasonable and mature 16-year old is usually cooperative Those under this age were given a general anaesthetic The CT was first lowered rather forcibly and even stretched and the medial aspect of the proximal end was examined At 16 such examinations a knot was seen On seeing this the assistant examined the eyes for a first degree nystagmus directed away from the operated ear and this was always present (Nystagmus was sought prior to the operation and was not present there has occasionally been a twitch only with the drugs used for sedation in this study they were Chlorpromazine Promezathine and Pethidine) In one bilateral case this knot was seen in both ears and in 2 unilateral cases in the operated ears Thus in these 3 cases the CTs were spared and they were cured These cases constitute the evidence that the essential part of the operation is the successful ablation of the LB or LBs

Results

There were 4 recurrences, and since the symptoms of their recurrence were eliminated by a second operation based on the conception embodied here a 100% *successful* result is claimed and is valid There was a satisfactory follow-up of nearly 2 years in the earlier cases and 1 year 7 months in the later cases of this series. After this the author moved to a larger older and better known hospital in the capital city 70 miles away Thereafter the follow-up was largely a negative one and so if necessary no claim to follow-up will be made at all for this latter period The patients had been instructed to contact the author by letter in the first instance if they developed any recurrent headaches. Since no intermittent contact was maintained with them during the intervening years it has not been possible to contact all of them by letter a few months ago However it can be stated that there is no known case of a recurrence either in this series or in any other series This includes cases treated in 1965 8 years ago some of whom are in contact with the author and are all well If recurrences occur they are of the nature to be described and it will be agreed that they would come to the notice of the author It will be seen that such recurrences readily agree to a second operation.

One case who had a unilateral operation in her right ear in early 1966 had contacted the author with recurrent headaches which were *mainly* left-sided which had occurred from about April this year She has recently had only her left LB ablated and she is now well Another patient a male of 31 years at the time of a unilateral operation in February 1966 remained well till early 1970 when he got what he calls an attack of collapse he subsequently had two further attacks one in 1970 and another in 1971 and has since remained free of them. Even after all these years he remembers that his headaches had been very severe He

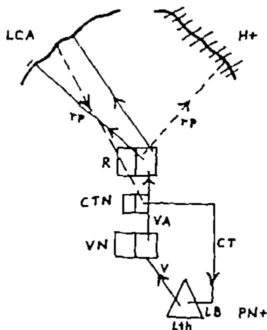


Fig 3 H+ PN+ Left-sided headache and PN Right irritable LCA. *Lth* labyrinth *V* vestibular nerve *VN* vestibular nucleus, *VA* vestibular afferents to ipsilateral *R* reticular area *rp* reticular-cortical projections (major contralateral minor ipsilateral). Connection of LCA to CTN (CT nucleus) CT and LB shown.

elaboration here The observations of Carmichael et al are well known and accepted as proven and it will be seen their results completely confirm the author's conception and postulation There is then an irritable LCA in the middle of the superior temporal gyrus and it is an effector area Directional sensitivity is not merely a prolonged sensation of vertigo but is a prolonged nystagmic movement of the eyes It cannot be contended that the sensory vestibular projection area does this It is known that nystagmus is the exception rather than the rule in vertigo i e there is a sensation of turning or unsteadiness without nystagmic eye movement why should a prolonged vertiginous sensation produce eye movement here?

Since one part of the postulation (the (LCA) is confirmed it is reasonable that the rest of the postulation is also correct and the effect is produced through the LB Further the conception set out here completely conforms to the requirements so ably anticipated by Carmichael et al (1956) of the neurological mechanism that can explain the phenomenon of directional preponderance or directional sensitivity of caloric nystagmus Here the tonus element has been identified its brain stem representation as required by them is at a different level from the vestibular representation They too envisaged a connection to the opposite temporal cortex (Fig 3) Here further is an explanation and a situation in which the tonus element is hyperactive on one or both sides When it is hyperactive on one side or more so on one side than the other directional sensitivity results How it can be hyperactive in other situations of vertigo will be touched upon and explained briefly Here then a hypothesis because it is corroborated in the manner described above has become acceptable as a scientific fact The LB is an integral part of the whole conception so there has to be and there is an LB It is evident that proof that when the LB is ablated this directional sensitivity is abolished (or markedly decreased) will readily be forthcoming Penfield (1954) stimulating the parietal lobe produced nystagmus an effector phenomenon so there has to be an effector area close to his point of stimulation

Treatment

At the time this work was done the method used to break the LB was to avulse the CT nerve with a fine hook as close to the annulus as possible There were 47 bilateral operations and 53 unilateral operations This series represents a rather high percentage of unilateral cases In a similar group recently treated the unilateral cases are a

caused blurring: one boy said there were occasions when he had diplopia while reading. All these symptoms ceased at operation. As far as the author knows there is no awareness of the fact that the disturbance which produces the PN of the type described here affects the vestibulo-visual fixation mechanism and leads to difficulty with continued reading.

Lacrimation

Lacrimation occurs sometimes as a result of reading or on looking at a bright light or at the sun, in one case the lacrimation was spontaneous. These too ceased.

Lack of concentration, defective memory, drowsiness

These, as said before, occur as symptoms in the recorded history of a very few patients in this series since they were not symptoms for the presence of which enquiry was made. Later however and in later series enquiry showed these symptoms to occur in varying degree in quite a high proportion of patients with these headaches. It is possible that if careful inquiry were made the figures might be as high as 60% particularly for drowsiness and lack of concentration, and what is more the symptoms cease with their operations.

Excessive sweating

This also occurs more frequently than has found representation in this series. Very occasionally the hyperhydrosis affects the palms and soles making manual work difficult. In one case with this troublesome symptom, the anticonvulsant Dilantin produced noticeable improvement, this when confirmed will lend support to the contentions the author will make here that these features are all manifestations of a minor epileptic process. At operation all excessive sweating ceases.

Fulness of the ear(s) and inexplicable itching

Intermittent fulness of the ear(s) was fairly often reported in this series since inquiry was always made about the hearing. Itching was infrequently reported but it is now evident that if it is inquired into minor itching is a fairly frequent accompaniment whenever there is hyperactivity of the LB mechanism. It is also now known that patients presenting with this symptom only and when nothing exceptional is found in the meatus have delayed taste (frequently over 20 seconds) and feeble PN. It represents a paraesthesia, and the implication also follows that the CT nerve gives off a branch to the meatus: this latter observation has been made before.

Recurrences

(A) Three cases after unilateral operation presented with a recurrence 2 weeks, 4 months and 15 months after the interference. The headache had shifted to the other side in 2 who had had tinnitus this too had changed sides and so too had the PN and the sway in Romberg's test. Two had their CT nerves avulsed and one had only the LB broken and they have remained well since. All 3 were caloriized in the manner described before their second operation also and though all 3 said that it was the second ear when tested which had made them more giddy the marked directional sensitivity seen in a newly presenting *unilateral* case was nevertheless not found; there appears to be a reason for this though it cannot be discussed here nor is it necessary.

(B) One patient who had a bilateral operation which had consisted of an avulsion of the CT nerve on the left and a successful breaking of the LB on the right, presented

was also one of the patients who had vomited with travel In his case a journey of over 10 miles would have brought this about. His operation had been a right LB ablation only and after it he had been com pletely free of headaches and also of any discomfort with travel After his attacks of collapse he is giddy with travel but not giddy otherwise He is apparently not very concerned about this since nausea does not occur except with very long journeys When he happened to mention this to the author in the middle of this year he was asked why he had not reported all this earlier and he replied that he had not thought that collapse concerned the author who had operated for headache His attacks seem to have been acute vertigo leading rapidly to a fall in blood pressure.

Other Results

Tinnitus

In 46 cases there had been a tinnitus and in all of them the tinnitus ceased immediately Only in one case a male of 43 years who had a bilateral operation and a bilateral tinnitus the tinnitus persisted in one ear It was however softer and of a higher pitch This patient was found to have early pres byacusis Though it was not inquired into at the time of this study and since it is now known and would constitute useful informa tion it may be stated that the tinnitus as sociated with the LB mechanism is always a low pitched one corresponding to the 125 cps tone of the PT audiometer The tinnitus is not a constant whine but an interrupted hum – hum – hum Occasionally a patient says that though it corresponds to the 125 cps tone it is a ho – ho – ho sound Very very exceptionally a patient says the sound is lower pitched than that and likens it to falling rain and this corresponds to a tone of 64 cps One patient who had a tinnitus in this series in one ear a week after operation said the sound had recurred and she was found to have a retracted drum this cleared up It is now known that such patients will liken the sound to the sound of surf on a tropical beach and this would apparently correspond to a tone of 32 cps Three patients who had unilateral PN had occasional tinnitus in the other ear this too ceased with the unilateral operation

Travel

Six patients had said that they had symp- toms of motion sickness and vomited on the limited travel they were wont to undertake Such travel was only of the order of 10 to 20 miles The adjoining country was hilly and the roads winding

This work when repeated in the coastal plains discloses about 3 to 4 patients in every 100 who actually vomit with limited travel These patients after their opera tions become totally changed for the better in their reaction to travel There is no equi vocation about this A few patients in this series said they got sick headaches with travel many said they tended to get a head ache with travel Three said they became a little giddy with travel and tended to be un steady when they got off the bus Many said they had no discomfort with travel In those who had any symptoms such symp- toms ceased at operation

Reading

Since most of the patients were peasants and labourers not many seriously com- plained of any difficulty with reading Among those who appeared to read to any extent (the complaints were thus com moner among students) there were instances of the letters blurring become squiggly and some said the lacrimation that occurred

acceptable upper limit of normal) at least, and to improve to 5 sec within a few days This also happened with the 16 CTs that were spared here return of taste took a varying number of weeks as is to be expected When in future studies only the LBs are ablated this will be found to be so in every case. The taste delay (before the operation) as said before is usually over 20 sec When the taste delay which improves dramatically is considered along with its association with the muscle contraction headache, which also has been cured, it will become acceptable and evident that the disturbance must have been epileptiform and must have occurred in the cerebral cortex. No other pathology or location is *feasible* particularly when the other associated symptoms are taken into consideration. With these evidence of another disturbance occurs in such cases and that is a central type of first-degree PN All that can be acceptably said at present with regard to PN is that it is evidence of a disordered or pathological link somewhere in the vestibular complex which becomes *manifest in the* activation process of a positional test This PN also must have a cortical origin because of the invariable association described here Nobody has suggested or would suggest that this PN is due to a disorder in the vestibular projection (sensory) area in the cortex By this reasoning alone there must be an *effector* LCA *There* is already substantial evidence in this study of its existence and of its location. *Taste* representation in the cortex Penfield & Jasper (1954) say is at the bottom of the post central gyrus (Fig. 2) deep in the Sylvian fissure on the superior bank above the insula and probably extending onto the insula. The location of the motor area which when affected by an epileptiform process can produce sustained muscle contraction of the scalp muscles is well known and is very nearby The LCA is also nearby and has to be nearby on the superior temporal gyrus The auditory sensory area is mainly in Heschl s gyrus (anterior transverse gyrus on the superior surface of the temporal lobe) on the inferior bank of the Sylvian fissure. Penfield & Jasper (1954) also say that there is evidence of vestibular representation adjacent to (and posterior to) Heschl s gyrus within the Sylvian fissure Though it is not necessary for the purposes of the author's thesis, it is suggested however and is likely to be accepted as being in fact so (from the evidence that emerges here) that the LCA extends into the Sylvian fissure onto the inferior bank and onto the surface of the insula Davis & Davis (1964) for instance say that the cytoarchitecture of the posterior part of the insula resembles that of the temporal cortex while that of the anterior part does not. The taste area and the LCA must be contiguous *The author wishes* to emphasize this and it will be *found to* be so that this central type of first-degree PN is always associated with delayed *taste* perception and is to be found in many vague conditions which must be called psychogenic. Nature has ordained this to be *so* *Nature* always works to an approved pattern. *It will be found in all* nausea there is PN and delayed taste perception. In mild nausea the PN will be feeble and taste delay will only be *of the order of 3* or *4* seconds but both will disappear when the nausea ceases. This arrangement will put an animal instinctively off its food when there is *nausea*, and this is beneficial particularly if *the* cause is alimentary It will be seen that for perhaps a good reason nature has ordained *that this LCA* is easily disturbed It is *evident* then how the various disturbances (Fig 2) that accompany these headaches occur To explain the sweating lacrimation, *etc* reference is made to *Van Buren (1958)* who says that the autonomic representation in *the* temporal cortex *is* to be *found in* the insula and mesial temporal region etc. The superior temporal cortex and the insula slope onto the mesial tempo-

after 8 weeks with a left sided headache A left PN and a sway to the left in Romberg s test was found The intact LB in the left ear was successfully ablated (a nystagmus followed) *in the manner to be described* and she has remained well since

Criticism

Bilateral avulsion of the CT *nerves naturally* affects taste perception but appeared to be satisfactorily adjusted to A more serious consequence is a dry mouth Curiously only one patient complained of this The author *however usually avoided discussing* any disabilities that resulted from such an operation So this may not give a true overall picture

Alternative Technique

If the CT nerve is only gently lowered (this is done in order to locate its proximal end) the knot that was described earlier will not be seen The proximal end of the nerve is in the vertical plane exactly midway between the stapedius tendon and the round window Occasionally it may be slightly higher or slightly lower than this but it is always below the tendon It is of course posterior to the *incudo-stapedial articulation* The posterior wall of the middle ear is now *scraped fairly firmly* with 3 or 4 vertical strokes from above downwards by introducing an angled instrument with a flat blade below the nerve The instrument the author uses is Rosen s annulus ring curette It would appear *preferable that the instrument* had a cutting edge With experience the CT need not even be lowered Unnecessary curettage to find the nerve appears undesirable since it may damage the nerve Occasionally the ablation of the LB has been done without seeing the CT Sometimes the only structure to be seen without undue curettage is the round window Successful ablation of the LB always *produces an immediate* brisk nystagmus There should be no difficulty in successfully ablating the branch under general anaesthesia, though seeing the nystagmus is satisfying Very *very occasionally there is no nystagmus* or merely a sort of wandering of the eyes on deviation Even in these rare instances a nystagmus develops later on though it may be feeble It is useful to mention that if a barbiturate such as Nembutal is used as a sedative there may be a nystagmus before *the operation* There is *no reason* why the incudo-stapedial articulation should be disturbed by this procedure Occasionally a mild facial palsy develops which always clears up in an hour or two

Discussion

It was found in this study in 19 instances where the nerve supply had evidently been *abnormal that* with the avulsion of the CT *taste perception had returned to normal* i e to within 5 sec the next day in every single case If not 5 seconds then to 7 sec (th

acceptable upper limit of normal) at least and to improve to 5 sec within a few days This also happened with the 16 CTs that were spared here return of taste took a varying number of weeks as is to be expected When in future studies only the LBs are ablated this will be found to be so in every case The taste delay (before the operation) as said before is usually over 20 sec When the taste delay which improves dramatically is considered along with its association with the muscle contraction headache, which also has been cured it will become acceptable and evident that the disturbance must have been epileptiform and must have occurred in the cerebral cortex No other pathology or location is feasible particularly when the other associated symptoms are taken into consideration. With these evidence of another disturbance occurs in such cases and that is a central type of first-degree PN All that can be acceptably said at present with *regard to PN is that it is evidence of a* disordered or pathological link somewhere in the vestibular complex which becomes manifest in the activation process *of a* positional test This PN also must have a cortical origin because of the invariable association described here Nobody has suggested or would suggest that this PN is due to a disorder in the vestibular *projection* (sensory) area in the cortex By this *reasoning* alone there must be an effector LCA There is already substantial evidence in this study of its existence and of its location Taste representation in the cortex Penfield & Jasper (1954) say is at the bottom of the post central gyrus (Fig. 2) deep in the Sylvian fissure on the superior bank above the insula and probably extending onto the insula. The location of the motor area which when affected by an epileptiform process can produce sustained muscle contraction of the scalp muscles is well known and is very nearby The LCA is also nearby *and has* to be nearby on the superior temporal gyrus The auditory sensory area is mainly in Heschl s gyrus (anterior transverse gyrus on the superior surface of the temporal lobe) on the inferior bank of the Sylvian fissure. Penfield & Jasper (1954) also say that there is evidence of vestibular representation adjacent to (and posterior to) Heschl s gyrus within the Sylvian fissure. Though it is not necessary for the purposes of the author s thesis it is suggested, however and is likely to be accepted as being in fact so (from the evidence that emerges here) that the LCA extends into the Sylvian fissure onto the inferior bank and onto the surface of the insula Davis & Davis (1964) for instance say that the cytoarchitecture of the posterior part of the insula resembles that of the temporal cortex while that of the anterior part does not. The taste area and the LCA must be contiguous The author wishes to emphasize this and it will be found to be so that this central type of first-degree PN is always associated with delayed taste perception and is to be found in many vague conditions which must be called psychogenic. Nature has ordained this to be so Nature always works to an approved pattern. *It will* be found in all nausea there is *PN and delayed* taste perception. In mild nausea the PN will be feeble and taste delay will *only* be of the order of 3 or 4 seconds but both will disappear when the nausea ceases *This* arrangement will put an animal *instinctively* off its food when there is nausea, and this is beneficial particularly if the cause is alimentary It will be seen that *for* perhaps a good reason nature has ordained that this LCA is easily disturbed It is *evident* then how the various disturbances (Fig 2) that accompany these headaches occur To explain the sweating lacrimation, etc. reference is made to Van Buren (1958) who says *that* the autonomic representation *in the temporal* cortex is to be found in the insula and *mesial* temporal region etc. The superior temporal cortex and *the insula* slope onto the mesial tempo-

ral cortex Penfield (1954) makes reference to his findings that disturbance in the insula can lead to nausea and other alimentary disturbances The itching that attention has been drawn to here (and the suggestion is made that it should always be inquired for) represents a disturbance in the sensory cortex adjacent to the taste area Intermittent *fulness of the ears and the tinnitus are* readily explained The headache itself is due *to disturbance in the bottom of the motor* area which controls the muscles of the head

To explain how the headaches commence and how they can be successfully treated instead of quoting experimental and other evidence here reference will be made to a comparable phenomenon for which an explanation is available and a reference may be made to the work that embodies this Behrman & Wyke (1958) clinically distinguish one variety of vertiginous seizures Vesti*bulogenic seizures they say are a type of* reflex epilepsy A spontaneously occurring severe labyrinthine disturbance sets up disorderly impulses in the vestibular afferent pathways on one side (Fig 3) and because the disturbance is severe a disturbance in both reticular areas in the brain stem results Each reticular area has a major connection to the contralateral cortex cerebri and a minor one to the ipsilateral cortex In this condition a massive *bombardment of the* cortex on both sides results bringing about *the ictal discharge and the seizure* There *is further evidence in this thesis of a general* and corroborative nature that this LCA is *easily disturbed Schiller & Hedberg (1960)* found PN in all their cases of lesion of the parieto-temporal lobe (*both in epilepsy and* tumour) The author (who works in a hospital for adults) happened to examine 3 children between the ages of 10 and 13 years during the past 2 months One his own son because he complained of a headache for no reason *another his dental colleague s* son who for the past month had been making *involuntary* expirat n gasps frequently (this is an example of a vague symptom which occurs with this PN) and found they had bilateral PN and taste delay of over 20 sec on both sides Another girl casually examined for vague throat *symptoms had* left sided PN and taste R 11 L over 20 sec None *of them were giddy nor unsteady* at all in Romberg s test Evidence that these *signs are to be found* in otherwise normal children will be readily forthcoming Two of *these children* described had developed an aversion to travel Jongkees (1960) refers to *the fact that PN* often occurs without giddiness and recognition of this is necessary *for the purpose of the author s thesis* Considering an unilateral left sided headache with a left PN the *disturbance is then in the right* LCA (Fig 3) In a subject such as the girl described above if she is so predisposed a *continuing disturbance of this nature stimu*lates the labyrinth abnormally through the *LB and a minor vestibulogenic effect results* Since it is minor the hypothesis is advanced that only the ipsilateral (left) reticular area is disturbed and this brings about increasing disturbance in the right LCA only initially sufficient one day to cause spread to the surrounding contiguous area of the cortex Later the pattern of recurrent headaches becomes established

This concept that the vestibulogenic feed*back is initially to the* LCA and that dizziness only occurs when there is spread to the vestibular (sensory) projection area is a new one and perhaps an important one The corroboration arising from Jongkees ob*servation referred* to above emphasizes its validity Later the pattern of recurrent head*aches becomes* established The pattern is well known and has been described here This keeps on *recurring and in those who* have a constant dull headache too there is a *constant involvement of the scalp muscle* motor area nearby The disturbance waxes and wanes spreading *and receding* as all epileptic processes are known *to do for* reasons which are *not clear* The process

continues and even old age may not bring relief (Graham 1963) What can be done about it? It will be evident that if the abnormal excessive vestibulogenic feed back is abolished by ablating the left LB in a left sided headache some benefit should accrue In this study this has been done and the headache ceased it will be seen that it should not thereafter recur either Since with this ablation the disturbance in the right LCA either subsides completely or sufficiently (see Recurrence B) that it no longer spreads hence thereafter there is no recurrence of headache and its accompanying symptoms whatever they may be from tinnitus to drowsiness and defective memory and nausea and vomiting. There must also be a good reason why the tinnitus is always low-pitched but this will not be discussed here. Taste perception should also return to normal and it will be found (and has been found even in this study) to return to normal i e perception in 5 sec in the test described Behrman & Wyke have drawn attention to the fact that each reticular area has a minor connection to the ipsilateral cortex Thus any evidence of a minor disturbance on the opposite side should also subside This was found to be the case. The taste finding in a unilateral case typically is R 13 L over 20 sec before operation and on the morning after the finding is R 5 secs L negative If the innervation had been abnormal the finding would be R and L 5 sec simultaneous. This explains why 3 unilateral cases had bilateral tinnitus and why there could be bilateral itching and why the symptoms in both ears cease with a unilateral operation The explanation is complete and by this very completeness by the method of science lends strong support to the entire concept. The findings in one case in this series provide further support A girl of 19 years with right-sided headache of 5 years duration had for 3 years or so two other features About once a month with her headaches and dizziness she used to fall on the floor and lie pale and still with clenched teeth unconscious for ½ an hour or so Also with the headache and giddiness she would have quite severe right sided colicky abdominal pain about twice a week. This pain could last one day sometimes though usually it lasted a few hours only After investigations her appendix had been removed a year previously without affording her relief After her ear operation both the akinetic seizures and her abdominal pain ceased and did not recur The latter took about 2 weeks to subside completely It is well known that both these are epileptic phenomena. Penfield (1954) has done temporal lobectomy and insulectomy for severe alimentary seizures Akinetic seizures will be found to accompany these headaches in about 3% of cases and severe inexplicable abdominal pain in 2% and less severe pain and flatulence to the extent of about 5 to 6% in all These will usually disappear with their ear operations or if not will be found to be greatly reduced

EEG was not done in the case referred to and was only done in 3 chronic cases and was found to be normal Perhaps activation procedures *prior to EEG may reveal* abnormalities in some cases as has already been found in migraine Blau (1971) refers to this and says the concept that migraine is epileptic is an old one

Further support for the entire conception is afforded by the following conditions and an explanation of their mechanism of production on the basis of this conception is enlightening that headache is often associated with vertigo is well known. Its association with Menière s disease has been referred to by Colman (1971) It is clear now why this happens In severe vertigo e.g. severe acute Menière what may be called collapse occurs The patient is found to be pale and cold and to look anxious and depressed there is sweating and salivation and even hyperventilation there is pain in the head nausea and vomit

ing The pulse is slow and the blood pressure low *Colman (1971) says that this is a* vagal effect It will be seen that the symptoms and signs are both parasympathetic and sympathetic *It is now clear how severe* vertigo through a vestibulogenic effect and feed back through the LBs leading to a circuit generating hyperactivity causes spreading excitation from the LCAs to the area of autonomic representation thus giving these features The conception of Behrman & *Wyke explains how in severe vertigo* both reticular areas become activated thus *leading to increased excitation in both LCAs* which may not be equal If the LB mechanism is very hyperactive spontaneous nystagmus can also occur (cf nystagmus on LB ablation) This excessive cortical activity leads in the rare predisposed subject to a seizure (Behrman & Wyke) and also in rare instances to unconsciousness alone (Golding Wood 1960) *This also explains why PN* has been found in Menière s disease why *directional* preponderance or *sensitivity has* been found in the caloric tests and why the nystagmus can be unpredictable and found to change direction (Colman 1971) and also why the sensation of turning or of falling is unpredictable and can be to either side (Golding Wood 1960) An explanation for these features has been difficult hitherto *Only the feature of excessive salivation has* not been explained here Penfield (1954) says the cortical area for salivation is at the bottom of the motor area nearby Arulpragasam (1967) found PN in the syndrome of vertigo and salivary gland enlargement and in recurrent parotitis These conditions he stated were due to excessive secretory activity engendered by an *epileptiform* process It is now known that in these conditions there is a taste delay thus placing the disturbance in the cortical area under consideration here It appears that hyperventilation can also be explained but will not be undertaken *What is less well documented is* the fact that in moderately severe vertigo a rise of blood pressure will be found Any *family physician will confirm that this is a* common occurrence His explanation for this will differ from what is advanced here It is *clear that spreading excitation in the LCAs* in moderately severe vertigo will bring the temporary elevation of blood pressure that has been so commonly *observed It is the* vertigo that brings about such elevation and not the elevated blood pressure the vertigo as it is now believed to be the explanation *Van Buren (1958) studying temporal lobe* epilepsy and the autonomic concomitants of *ictal automatism* found rise *of blood* pressure tachycardia lacrimation retching flushing of the face swallowing and other changes relevant here. A recorded fall in blood pressure did not occur among his cases but he gives an explanation of why this may not have been recorded He came to the conclusion that there is probably *spatial separation of the representation of* autonomic function in the temporal cortex *A delay in taste perception must occur in* the situations discussed here

Wood & Graybiel (1973) say the symptoms of motion sickness vary with the individual although in a given individual the same pattern of signs and symptoms will follow repeatedly They may include any or all of the following drowsiness yawning salivation swallowing hyperventilation headache and flushing followed by pallor of increasing intensity Cold sweat on the forehead underarms hands and around the mouth is frequently observed Increasing nausea may lead to vomiting *To this the* author adds minor itching of the ears and *fulness of the ears during the nausea* In nausea there is a bitter taste in the mouth and it will not be surprising if taste perception will be found delayed that there is a PN in acceleration deceleration and stoppage of movement is well known How the disordered vestibular afferents in motion *bring about an excitation of the LCAs* and the neuronic *circuit described here will*

further stimulate the labyrinths and through a vestibulogenic effect bring about spreading excitation from the LCAs is clear It will be noticed that these symptoms and signs strongly resemble those found in the muscle contraction headaches and the state of collapse of a severe Menière's attack If as in the headaches the neuronic circuit is broken, relief should follow This can be achieved in two ways one is to destroy the labyrinth or the afferents on both sides and that this will bring relief has already been found (e g. deaf mutes with defective labyrinths react differently when tested Wood & *Graybiel 1973)* The other way is to ablate the LBs There is some evidence in this study itself that this will prove beneficial Since fresh light on the subject of motion sickness is eagerly being sought particularly at the present time the following experimental evidence can usefully be juxtaposed since it will be found to support the views expressed here Jongkees (1960) citing the experimental work of Fernandez et al says that the lesions of the nodulus cerebelli in the rabbit give PN which disappeared when the labyrinth was destroyed Keel & Neil (1966) record that electrical stimulation of the flocculonodular *lobe of the cerebellum* brings about evoked potentials in the ecto-sylvian gyri of the cat and the dog, and comment on how extensive the vestibular representation in the cortex is (This in itself is evidence for the LCA and its *location*, since the cerebellum is not known to have connections with sensory areas *of the cortex* Its function is to suitably modify corticofugal effector effects.) These authors also state that the auditory sensory area *in* these animals is in the ecto-sylvian *gyri* Hence it follows that the ecto-sylvian gyri *in these animals* correspond to the LCA and Heschl's gyrus *in* man. Then they say that if the nodulus cerebelli is removed *in a dog*, the animal cannot thereafter be made to become motion sick.

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comes dazed PN and delayed taste perception (of over 20 sec) will be found In the mild cases at any rate these will be found to cease with recovery It is evident what the post-concussional syndrome is The symptoms resemble the muscle contraction headache closely Cabraal (1972) says that it is a puzzling condition It would appear that the puzzle has been unravelled The youngest case in this series was evidently in retrospect a case of post-concussional syndrome. When corroboration that the post concussional syndrome is what it is suggested here to be is established it would constitute powerful support for the views advanced here and elevate these views from merely being an acceptable hypothesis into something else again It is well known that sustained muscle contraction is the main cause of the headache in the post-concussional syndrome and dizziness defective memory and anxiety are also listed among the symptoms (Mayer-Gross et al 1960) It is for this reason (that the LCAs are easily disturbed) that the functional headaches are so common and both vascular and muscle contraction headaches are due to a derangement of a mechanism which includes the LCA It will be agreed that this is a logical development

Vascular headaches

While PN and delayed taste will be found to occur during the headache they may not be present when the patient presents for treatment From what has arisen here the ear to be operated on would be the one on the headache side Since the headache is usually unilateral only one ear need be operated on usually It is suggested that the severe status *migraine and cluster headache* be first considered for treatment They will present with a headache and the relief afforded therefore dramatic Since it appears to have been established that in the vascular headaches the immediate cause of the headache is a contraction and dilatation of the intra and extra cranial blood vessels it need only be postulated that in the people predisposed to these headaches there is an intermittent spread of excitation from the LCA to an area of autonomic representation nearby on the temporal cortex which controls the calibre of these blood vessels.

It is evident that in this work in 47 cases *direction-changing PN and in 53 cases* direction-fixed PN have been abolished Hence an acceptable deduction can be made about their mechanism of production Since Aschan (1960) inclines to the view that with alcohol ingestion the PN is a peripheral effect *it is likely to be found that alcohol* PN is also produced by this mechanism

It would appear that the validity of the concept that each temporal *lobe* is connected to the opposite labyrinth by a LB of the CT nerve is established there is a labyrinthine branch

Summary

The conception of headaches with positional nystagmus *(PN) has been used here to* describe the common troublesome and fre*quently recurring* and spontaneously occurring muscle-contraction headaches Two new signs are described with regard to them PN and delayed taste perception on the anterior two-thirds of the tongue to the *application of* moist salt crystals It was *shown that the PN can be made to* disappear and that taste perception could be expected to return to normal when these patients were treated in the manner described *On the basis of a certain as yet* unaccepted *neuro-otological* conception and by using a minor otological surgical

interference it was possible to cure 100 consecutive cases of these headaches and thus come to a conclusion as to their mechanism of production. Anticipating the likely importance and also because their mechanisms of production are likely to be found to be akin to the mechanism discussed here acceptable hypotheses are set out here about Motion Sickness and the Vascular Headaches It will be recognised when what has been said here is substantiated by other investigators that this will represent the cure for all known recurrent troublesome functional headaches both muscle-contraction and vascular This would have become possible as a result of the author's conception that there is a connection between one temporal lobe and the opposite labyrinth through the labyrinthine branch of the chorda tympani nerve The results here described alone would constitute overwhelming evidence that there must be and there is such a labyrinthine branch In this early study made in 1966 the chorda tympani was avulsed at a certain point in its course in the ear in order to break the labyrinthine branch Even in this series 3 patients were cured when the author had satisfied himself at operation, that the branch had snapped and the chordas themselves were therefore spared It is useful to state also that this procedure has been subsequently used with ablation of the labyrinthine branch or branches only with the same satisfactory results The procedure for such ablation is described here, thus obviating the necessity of making another report on the same subject.

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Dr A C Arulpragasam F R C.S E.
77 Ward Place
Colombo 7
Sri Lanka (Ceylon)

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Introduction

Over the past several years many children with speech and language disorders have been referred to the Pedoaudiological Clinic at the St. Gallen Kantonsspital. A number of these children have language problems which may be attributed to profound hearing losses. Obviously a child who can not hear the sounds of speech will not learn to talk. Other defects of an organic nature, such as cerebral palsy, may interfere with the production of speech sounds. These children may learn to understand speech sounds but be unable to perform the highly complex motor patterns to produce them. Some children are mentally retarded to such a degree that they have not reached the required psychomotor level of development necessary for language acquisition.

Thus there are many causes for speech problems in children. However, there are some cases whose speech and language difficulty can not be attributed to peripheral sensory disorders, structural deformities, motoric dysfunction or mental retardation. Such clinical cases are the focus of this study. Therapists working with this group have the impression that these children differ from normal children not just in their failure to develop adequate speech and language skills, but even more in non-verbal behavior. Then too, clinical observation gives the impression that the clinical group may not be homogeneous for some appear to have a serious lag in symbolic performance while others do not.

As a consequence of these observations a preliminary research effort was organized to investigate the clinical group. It was hoped that research would lead to more exact studies in the future. This article reports on the results of this preliminary research.

Problem

Specifically, two questions were posed. First, what characteristics differentiate these handicapped children from normal children of the same age. Secondly, are the handicapped homogeneous or composed of subgroups or so individualistic that no classificatory principle can be found?

Methods and Procedures

The general research plan followed in this study consisted of two steps. First, a normal group of children was compared to a clinical group. Secondly, comparisons were made within the clinical group. Both groups were observed on a series of tasks thought on the basis of clinical observations to be critical in distinguishing between and [illegible] groups. Since few standardized tests can be given to language-disturbed children [illegible]

[illegible]

(SON) to evaluate their ability to structure and reproduce visual patterns Finally two visual tests paralleling the acoustic dimension analysis and sequence discrimination were administered In the first of these a same or different judgment was required in the discrimination of the color and size of two rectangles A similar judgment was required in a test of the ability to discriminate visual sequences composed of two colors and two sizes of rectangles in various combinations (Affolter et al 1974)

Gene al behavi r

The evaluation of general behavior was based on testing direct observation and with the clinical group on video tape recordings of the child Attention span the child's ability to focus on a timulus for a length of time is the first general behavior presented here At this point observations were not concerned with the nature of the task or the specific nature of the stimulus Children with short attention spans start many activities but complet few Such children may appear hyper active s they change one toy for another or run from game to game Observations such as the length of time a child pursued a partic ular task the number of different toys played with and the number of tasks completed were used to evaluate attention span

Another aspect of general behavior anticipation, requires the child to integrate a series of successive activities Evaluation of anticipation was based mainly on clinical observation Howe er with the younger children and with the se erely handicapped children a task from the Borel Maisonny (1963) test was adapted The ta k referred to here was the beads-tube task In thi case it was used as a means of ev king responses f r observational purposes In the bead tube problem the examiner pa ses a tring of bead through a wooden tube A normal child will watch for the beads to emerge from the bottom of the tube when the examiner insert the beads at the top Often the child will put out his hand to catch the beads Children with anticipation problems seem surprised when the beads reappear Play audiometry also allows observation of anticipation In play audiometry the child is expected to select a part of a game hold it to the loudspeaker remove the part at the sound of a tone and then proceed with the game Another aspect of general behavior is hand-eye-coordination and body-eye-coordination This requires hand movements to be guided by visual monitoring as for example inserting a key into a lock However it may be used in a broad sense to refer to visual guidance of body movement as when picking up objects from the floor This ability was observed using play activities of varying difficulty such as simple block constructions as opposed to intricate close-fitting puzzles Shifting behavior was evaluated also Shifting requires that one change his point of view or his on-going activity For example a child must shift when requested to change from sorting on the basis of form to sort on the basis of color It was found that portions of non verbal tests could be adapted to permit observation of the ability to shift

Elaborative functions

Elaborative functions refer to performance which is characteristic of intelligent behavior in the sense used by Piaget (1947) In his genet ic theory Piaget considers intelligence to develop in a number of stages The first stage is the sensory-motor the second is the intuitive then the pre-operative next the concrete and then the formal intelligence stage The formal level is characteristic of children older than 1 years so this research includes only the earlier levels since the oldest children studied were only ten Inasmuch as the clinical group of children was seriously delayed in language development the intuitive and pre operative stages were emphasized for these levels are characterized by language acquisition Furthermore since some children in the clinical group appear to lag behind or even lack symbolic function emphasis was also

also to use clinical observation As an aid to observation periodic video tape recordings were made of the children s behavior These tapes were reviewed analyzed and evaluated by a team of trained audiologists speech therapists and psychologists on the clinic s professional staff

Subjects

Thirty subjects were selected for the clinical group from children under longitudinal observation at the Pedoaudiological Clinic This group ranging in age from three to ten years was representative of children whose sensory deficit if existent or mental retardation did not appear to account for their language problem For example this group included some deaf children who appeared to be more language handicapped than other deaf children of the same age and history

Another group of thirty children matched in age to the clinical group made up the normal group of subjects in this study These children were considered normal if they were progressing in a public school or kindergarten program without difficulty or in the case of younger children if they scored in the normal category of a non verbal intelligence test Several of the normal group were siblings of children in the clinical group and were consequently of a similar socio-economic level The remainder of the normal group were children of hospital personnel or their relatives

Between groups comparisons

Tests and observations

Overall four types of information were collected on the two groups of subjects The first type input consisted of evaluations of the child s auditory and visual acuity In addition the child s ability to discriminate auditory and visual dimensions patterns and sequences was tested whenever possible The second type general behavior consisted of observations of the child s behavior in various dimensions such as ability to concentrate to anticipate to exercise caution and other behavioral traits The third type elaborative functions consisted of evaluation of the child s performance on sensory-motor operative and figurative tasks The fourth speech sound production consisted of evaluation of speech sound production and ability to imitate speech sounds The specific tests and observations are presented below

Input audition

All children in both groups were assessed for hearing sensitivity by pure tone audiometry Play audiometry was used with pre school subjects to establish thresholds for the frequencies 250 to 6000 Hz. Whenever the child would not accept headphones free field tests were used to establish binaural thresholds For older subjects standard pure tone audiometry was used to determine thresholds for the frequencies 125 to 8000 Hz (criterion for normal hearing was an average air-conduction threshold of less than 20 dB (re HL ISO) at the frequencies 500–4000 Hz)

Speech audiometry was used to obtain speech discrimination scores on those subjects able to respond (criterion for normal speech discrimination was an intelligibility score of 100 percent at 63 dB re SPL) A test of acoustic dimensional analysis followed which required the children to make a same or different response to two different frequencies and two different intensity levels A similar judgment was required in a test of discrimination of acoustic sequences combining two frequencies and two intensity levels in various patterns

Input vision

Ophthalmologic referrals were made for all subjects suspected of having visual difficulties Older children (ages 5 to 10 years) were given the mosaic subtest of the Snijders Oomen (1964) non verbal intelligence test

Hz, a measurement of time can be made so that the rate of speaking can be cal culated

Plug-in component the Kay model 6016 C scale magnifier permits the expansion of selected portions of the voice spectrum so that individual harmonies can be identified From this the change in vocal frequency over time can be seen and the intonation contour of the utterance observed The older children were asked to say Ich gehe über die Strasse and Sprechen Sie Deutsch?" The question was replaced by "Was machst du for the younger children All of the normal group and part of the clinical group were recorded live voice The remainder were recorded on audio-tape from which selected cases were used for spectrographic analysis The audio-tapes were used also for phonemic analysis of the child s speech

Within groups comparisons

The previou ection presented the methods and procedures by which it was attempted to determine what characteristics of the clinical group differentiated them from normal children of the same age This section describes the methods and procedures used to determine if the clinical group was homogeneous or composed of subgroups or so individualistic that no classificatory subgroups could be formed.

Clinical observations of the clinical group had gi en the impression that some of this group lagged or perhaps lacked symbolic function So the clinical group was divided on the basis forming two subgroups The first ubgroup A was composed of 18 children who appeared clinically to have symbolic function The second subgroup B consisted of I children who appeared clinically to be seriously etarded in or lacking symbolic function

Again the children performances were studied This time the basis upon which tasks were selected stemmed mainly from clinical observation and Piaget s genetic theory More specific subtasks were formed to permit more detailed observation of the performances of the two subgroups. For example genetic theory and clinical observations suggest that aspects of general behavior and elaborative function may discriminate within the clinical group so these performances were studied in a more specific fashion

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Anticipation was divided into several as-

given to the sensory motor stage considered as a prerequisite for symbolic function

Information concerning the sensory motor and intuitive level was collected by observing direct imitation Direct imitation the ability to reproduce an activity at the moment or immediately after the original is produced marks the end of the sensory motor period (Piaget 1945) Therefore disturbances of this stage should be reflected in problems of direct imitation Deferred imitation the ability to reproduce an observed activity after a period of time has elapsed since the production of the original activity marks the beginning of the next stage If a child fails to develop deferred imitation it can be argued that he has not reached the intuitive stage Consequently observations of imitative behavior were considered significant in this research From the end of the sensory motor stage on there is an increasing differentiation of figurative processes and operative processes One of the most marked of the figurative processes is language which the child discovers by the middle of the second year Drawing performances can be considered an important expression of figurative processes in the older child and may be studied by observations of spontaneous drawings (Piaget *et al* 1948) The criterion for judging appropriateness was the age of the child beginning to draw If the child had no graphic expressions by the age of 5 years his performance was considered inappropriate Therefore one can study figurative processes in the child by observing his language and drawings Operative processes may be evaluated by scores the older child obtains in the SON sorting subtest For younger children this was accomplished by using the puzzles of the Borel Maisonny battery

Superficial observations of the severely handicapped children of the clinical group often give the impression that they are mentally retarded To investigate if the clinical group differs from the normal group because of mental retardation two kinds of information were collected First the linearity of the SON subtests was considered In intelligence testing it is assumed that a child scoring at the eight year level on one subtest will score at the eight year level on another That is to say the normal child s scores on various parts of the overall test will be consistent and present a linear profile without discrepancies The mentally retarded will show the same linear profile except that the level will be two or three years lower than the chronological age would indicate To investigate the linearity of such a profile in the groups three subtests of the SON-battery were used the mosaic memory and sorting subtests If the difference between any two of these tests was more than one and one half years the profile was considered non-linear Another way of investigating the problem of retardation raised above is to collect information about the linearity between operative and figurative processes and the relationship between direct and deferred imitation According to Piaget direct imitation marks the end of the sensory motor stage and deferred imitation marks the next higher level the intuitive stage (Piaget 1945) Therefore one would not expect a child to perform better in deferred imitation than in direct imitation It can be expected that a mentally retarded child will present a linear profile of retardation in operative and figurative processes and will also show better performances in direct imitation and poorer in deferred imitation

Speech sound production

Speech sound production was studied by means of a Kay Electric model 6061 B spectrum analyzer The Kay machine converts spoken sounds into a visual graph (a spectrogram) of frequencies and intensities as a function of time In general frequencies above 3 000 Hz are associated with consonants while vowels appear as bands of energy (formants) below 3000 Hz. From the spectrogram which covers a range from 100 to 8 000

Hz, a measurement of time can be made so that the rate of speaking can be calculated

Plug-in component the Kay model 6016 C scale magnifier permits the expansion of selected portions of the voice spectrum so that individual harmonics can be identified From this the change in vocal frequency over time can be seen and the intonation contour of the utterance observed The older children were asked to say Ich gehe über die Strasse and Sprechen Sie Deutsch The question was replaced by "Was machst du for the younger children All of the normal group and part of the clinical group were recorded live voice The remainder were recorded on audio-tape from which selected cases were used for spectrographic analysis. The audio-tapes were used also for phonemic analysis of the child s speech

Within groups comparisons

The previous section presented the methods and procedures by which it was attempted to determine what characteristics of the clinical group differentiated them from normal children of the same age This section describes the methods and procedures used to determine if the clinical group was homogeneous or composed of subgroups or so individualistic that no classificatory subgroups could be formed.

Clinical observations of the clinical group had given the impression that some of this group lagged or perhaps lacked symbolic function So the clinical group was divided on this basis forming two subgroups The first subgroup A was composed of 18 children who appeared clinically to have symbolic function The second subgroup B consisted of 1 children who appeared clinically to be seriously retarded in or lacking symbolic function

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The previous section presented the methods and procedures by which it was attempted to determine what characteristics of the clinical group differentiated them from normal children of the same age This section *describes the* methods and procedures used to *determine* if the clinical group was homogeneous or composed of subgroups or so individualistic that no classificatory subgroups could be formed.

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Anticipation was divided into several as

pects Clinically it is thought that in order to move adequately in a complex situation the child must integrate and anticipate a series of successive events For example consider a task such as putting an assembled wooden jig saw puzzle back into the game closet Here the child must pick up the completed puzzle carefully so as not to spill it hold it even while walking to the closet avoid bumping into objects which would jar the puzzle loose open the closet without spilling it and slide the puzzle into place without knocking it apart Another form of anticipation is seen on the Borel Maisonny beads-tube task Here it is expected that the child anticipates the emergence of the beads after they have been inserted and will be seen to avert his gaze to the bottom of the tube If the child catches the beads in his hand the performance can be considered tactile–kinesthetic–visual Anticipation is thought to be involved in play audiometry Here the task is a tactile–kinesthetic–auditory activity In play audiometry the child must pick up a puzzle piece or toy place it on the loudspeaker hold it there putting it down only after he hears the tone

Precautionary moves such as those taken when the child sees a large strange dog or when crossing the street presuppose previous tactile–kinesthetic experience The expectancy of danger is monitored visually and reacted to in a tactile–kinesthetic manner i e by running away Consequently observation of whether the child exercises reasonable caution is significant Initial stupor is defined as a brief interruption of ongoing activity when an unknown person enters a room or a brief hesitation when the child confronts a new situation As with precautionary moves initial stupor indicates that the child has learned from past experience He inspects newcomers visually for the presence of any threat that would call for tactile–kinesthetic reaction Children with problems of initial stupor may not interrupt their activities or they may overreact and flee from the situation Eye contact may be similarly interpreted

Body–eye (or hand–eye) coordination was also studied The child s ability to perform complex motor tasks requiring tactile–kinesthetic coordination such as climbing is considered clinically significant Through vision the child acquires information concerning the object he is climbing his actual movements are monitored tactually–kinesthetically

Shifting behavior was defined as a difficulty in changing a point of view or an ongoing activity More detailed aspects were observed for the within group comparison Observations of stereotyped movements were collected For example some children will rock back and forth spin an object or voice a syllable almost endlessly Another category concerned compulsive behavior Compulsive behavior is an activity with objects which appear to dominate the child For example a child may have to take all of the keys or collect all of the toy cars or line up objects in a certain way before one can work with him

Elaborative performances

In the previous section it was pointed out that aspects of three stages of intelligence (in Piaget s sense) were investigated the sensory motor the intuitive and the preoperative stages To inquire about sensory motor integrity and the beginning of intuitive intelligence imitative behavior was studied Observations of language and drawing performances were thought to give information about figurative processes and sorting performance to give information about operative processes The linearity of scores on some subtests of the SON battery and the discrepancy between the success of direct imitation and deferred imitation were considered to give some basis for discussing the problem of mental retardation It was considered that such data would be sufficient to differentiate the clinical group from the normal group However clinical observation leads to the assumption that for

comparisons of elaborative processes within the clinical group more detailed information would be needed. Therefore each stage of intelligence was divided into more aspects by referring again to Piaget's genetic findings

Instead of taking imitative behavior as the only representative of the sensory-motor stage more elementary processes were studied Perceptual intermodality performances were investigated by observing localization responses Music and animal calls were presented through two loud speakers to the right and to the left of the child If when a child heard the sound he turned his head in direction of the sound source to look at it the response was considered appropriate

Piaget considers that modality specific performance develops prior to perceptual intermodality performances For example a child will explore an object separately by tactile or visual means or a sound by auditory means before he can relate the different modalities Consequently listening behavior and visual matching of simple figures or forms were considered to yield relevant information about modality specific performance of vision and audition Figurative processes include several aspects according to Piaget. Language and drawing performances were studied This time children of subgroup A and subgroup B older than 5 years were compared on the basis of whether or not they had acquired some graphic expressions Besides language and drawing as two expressions of semiotic function, symbolic play and the use of pictures or picture recognition also depend upon the presence of semiotic function Therefore it was thought that observations of picture recognition and symbolic play would give important insight into the development of semiotic processes in the clinical cases Symbolic play behavior in the younger children was studied by presenting them the "bowl" of the BM-battery The bowl includes a number of small objects such as a car a cup spoon and plates a church *and a house* The child's play behavior with the toys was observed Do the objects have some meaning for the child does he handle *them symbolically* For example the car is to drive around the cup to be put on the plate the spoon to eat something from the plate Other clinical observations about the child's symbolic play behavior included reports from parents about the child's play behavior at *home* Furthermore the child's speech production was observed for meaning Does the child attempt to communicate with the few speech sounds he has acquired?

In the previous section operative behavior was studied by observing sorting performance In the within group comparison attention was focused on the nature of the task material *For example* the geometric forms sorting task of the SON was considered to be a visual performance without symbolic meaning *involved* On the other hand the child's performance on the jig-saw puzzles was considered as a tactile–kinesthetic task.

Results and Discussion

Between groups comparisons

Input

The first observations collected on the normal and clinical group were concerned with input functions Basically *the focus* here was to determine if the auditory and visual mechanisms were functioning within normal limits The input results shown in Table I are presented as the number of subjects in parentheses and as percentages of the group Thus the dash in the first cell of the columns to the left means that none of the normal children were unable to be tested for pure tone

Table I *Input between groups (numbers of subjects and percentages)*

NT=not tested (no information) T=tested (information) App =appropriate Inapp = inappropriate SON Snijders-Oomen non-verbal intelligence scale

Normal group		Clinical group			Normal group		Clinical group	
NT	T	NT	T		App	Inapp	App	Inapp
				Audition				
–	(30) 100%	(7) 23%	(23) 76%	Pure tone threshold	(27) 90%	(3) 10%	(8) 35%	(15) 65
(7) 23%	(23) 77%	(24) 79%	(6) 20%	Dimensional analysis of acoustic stimuli	(22) 96%	(1) 4%	(4) 67	( ) 33%
(8) 26%	(22) 73%	(24) 79%	(6) 20%	Speech discrimination	(17) 77%	(5) 23	(5) 83%	(1) 17%
				Acoustic sequences				
(10) 33%	(20) 66%	(23) 76%	(7) 23%	(*a*) comparison of two-element patterns	(17) 85%	(3) 15%	( ) 29%	(5) 71%
(17) 56%	(13) 43%	(28) 9 %	( ) 7%	(*b*) comparison of three-element patterns	(1) 9 %	(1) 8%	(1) 50%	(1) 50
(19) 63%	(11) 36%	(29) 96%	(1) 3 %	(*c*) comparison of four-element patterns	(11) 100%	–	–	(1) 100%
				Vision				
(15) 50%	(15) 50%	(7) 89%	(3) 10%	Ophthalmological result	(15) 100%	–	–	(3) 100%
–	(30) 100%	–	(30) 100%	Visual acuity: Clinical observation	(30) 100%	–	(7) 90	(3) 10%
(7) 23%	(23) 77%	(1) 69%	(9) 30%	Dimensional analysis of visual stimuli	( ) 96%	(1) 4%	(6) 67%	(3) 33%
(5) 17%	(25) 83%	(15) 50%	(15) 50%	Mosaic SON	(19) 76%	(6) 4%	(5) 33%	(10) 67%
				Visual sequences				
(11) 36%	(19) 63%	(4) 79%	(6) 20%	(*a*) comparison of two-element patterns	(16) 84%	(3) 16%	(4) 67%	( ) 33%
(17) 56%	(13) 43%	(26) 86%	(4) 13%	(*b*) comparison of three-element patterns	(1) 92%	(1) 8%	(1) 25%	(3) 75%
(19) 63%	(11) 36%	(7) 89%	(3) 10%	(*c*) comparison of four-element patterns	(11) 100%	–	(1) 33%	( ) 67%

thresholds Therefore the entry of 30 the total number of the normal group in the second cell *indicates that all normal children* could be tested In the clinical group seven children or 23% could not be tested They failed to learn the rules for play audiometry (This failure will be analysed in detail in the discussion about differences within the group) Twenty three (76%) of the clinical group could be tested The four columns to the right of Table I present the results for the children who could be tested The first two columns on the right present the results for the normal children tested The second two columns are the results for the clinical children tested *The terms appropriate* or inappropriate were used to indicate whether the children s responses were within normal limits A response was judged inappropriate by the research team if it fell outside the normal range or if it attracted the research team s attention alerting them to possible problems For the normal group 27 children (90%) gave pure tone thresholds within normal limits Three children (10%) did not meet *normal expectancies* ...

ing conductive hearing losses which were treated medically afterwards Eight children (35%) of the clinical cases presented normal thresholds 15 children (65%) did score inappropriately Eleven had a severe hearing loss belonging to the group of deaf children included in the research Four had a hearing loss of a conductive nature and received medical treatment.

Fifty percent of the normal children had normal visual acuity as evaluated by traditional screening procedures in their schools Reports of the parents and observations in the clinic pointed out that the other 50% did not appear to have difficulty in visual acuity Three of the clinical cases had ophthalmological examinations Two of them wear glasses one child is still under ophthalmological observation Twenty-seven (89%) of the clinical cases had had no medical eye examinations However their parents and therapists reported no visual particularities

Seventy-seven percent of the normal group could be tested on analysis of acoustic dimensions 71% on visual analysis The children who failed to take these tests were unable to give appropriate responses because they were too young less than four years of age Scores were within normal limits *for 96% of* children tested on auditory and visual analysis One child failed to perform adequately on visual analysis another child on auditory analysis

Only 70% of the clinical group could be tested on auditory analysis 30% on visual analysis The number in the not tested column were clinical children who were either too young or unable to respond adequately *because* of the severeness of their handicap About one-third of those tested scored inappropriate on both auditory and visual analysis Their failures appear to be *due* more to the difficulty of understanding the task than to a specific problem of dimensional analysis

Speech discrimination could be evaluated in the 22 children of the normal group who were older than 6 years of age Five children (23%) gave inappropriate responses They needed more amplification than the other children to achieve a score of 100 percent correct responses or they failed to reach a 100% level However for pure tone thresholds these five children had scored appropriately

Only 6 children of the clinical group were able to take the test for speech discrimination The other children were either too young or too severely hearing-impaired or lacked the necessary speech skills to take the test Of the tested children only one child scored inappropriately thus giving a higher percentage of success in the clinical group than in the normal group Different results are found in the visual test the SON *mosaic test* Here more children in both *groups could be* tested than in the speech *discrimination test* since the mosaic test is applicable *to a* younger age range than the speech-discrimination test and is of a non-verbal type On the visual test the percentage of failure in the normal group is about the same as that found for speech discrimination Six children (24%) *failed the visual* problems while 5 children (23%) failed the auditory problems *Of* the clinical cases 67% responded inappropriately However since *more clinical children* were exposed to this non-verbal task than to the speech discrimination task it is to be *expected that* more children would fail Inappropriate as used here does not mean that these children have visual difficulty but rather that *they* failed to adapt to the test situation a finding confirmed by the therapists *judgments*

The results of the sequencing tasks point out that the number of children who *could be* tested became smaller as the difficulty level increased from task (*a*) to task (*c*) *for both the* normal and clinical groups This trend in the normal group is about the same for the auditory *and the visual tasks* In the clinical group the number of non-tested children is higher for the acoustic series than for the visual series

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				Vision				
(15) 50%	(15) 50%	(27) 89%	(3) 10%	Ophthalmological result	(15) 100%	–	–	(3) 100%
–	(30) 100%	–	(30) 100%	Visual acuity Clinical observations	(30) 100%	–	(27) 90%	(3) 10%
(7) 23%	(23) 77%	(21) 69%	(9) 30%	Dimensional analysis of visual stimuli	(22) 96%	(1) 4%	(6) 67%	(3) 33%
(5) 17%	(25) 83%	(15) 50%	(15) 50%	Mosaic SON	(19) 76%	(6) 4%	(5) 33%	(10) 67%
				Visual sequences				
(11) 36%	(19) 63%	(24) 79%	(6) 20%	(*a*) comparison of two-element patterns	(16) 84%	(3) 16%	(4) 67%	( ) 33
(17) 56%	(13) 43%	(26) 86%	(4) 13%	(*b*) comparison of three-element patterns	(1) 9 %	(1) 8%	(1) 25%	(3) 75%
(19) 63%	(11) 36%	(27) 89%	(3) 10%	(*c*) comparison of four-element patterns	(11) 100%		(1) 33%	( ) 67

thresholds Therefore the entry of 30 the total number of the normal group in the second cell indicates that all normal children could be tested In the clinical group seven children or 23% could not be tested They failed to learn the rules for play audiometry (*This failure will be analysed in detail in the discussion about differences within the group*) Twenty three (76%) of the clinical *group could be tested The four columns to* the right of Table I present the results for the children who could be tested The first two columns *on the right present the results* for the normal children tested The second two columns are the results for the clinical children tested The terms appropriate or inappropriate were used to indicate whether the children s responses were within normal limits A response was judged inappropriate by the research team if it fell outside the normal range or if it attracted the research team s attention alerting them to possible problems For the normal group 27 children (90%) gave pure tone thresholds within normal limits Three children (10%) did not meet normal expectancies present

span caused by even slight increases in complexity of a problem of a room of a situation or of the child s physical condition or even the therapist s attention appear to differentiate the clinical children from the normal children.

Anticipation was judged inappropriate in all children of the clinical group thus differentiating them from the normal children Parents report that these children have difficulty in situations where it is necessary for them to wait Observations in therapy offer strong corroboration of such reports These children have difficulty in waiting at the work table until the therapist brings new work material They stand up and move around without focusing on a specific task These children want to leave immediately at the end of a therapy session. If such a child is told about a future event or activity he expects it to happen immediately Children of the clinical group who were tested on the *Borel-Maisonny scale* demonstrated difficulty in *anticipating the* emergence of the beads from the tube They looked at the upper end where the beads were inserted rather than anticipating them at the lower end When the beads appeared at the bottom the children seemed to be surprised. Children from the clinical group *did not reach for* the beads at the lower end of the tube The previous finding that play audiometry was unsuccessful with 23% of the clinical group appears to be related to anticipation problems For example in play audiometry the child must select a puzzle part, hold it against the loudspeaker wait for the tone, remove the puzzle piece fit it into the puzzle and take another piece to continue the game The clinical children seemed to forget what came next in this series of activities

Similar to the attention span are the observations about changes in body–eye or hand–eye coordination In a similar vein, there is never complete lack of hand–eye coordination in the clinical group In the clinical group coordination was less stable than in the normal group when the level of difficulty of a task was increased For example in assembling a jig-saw puzzle which he has already mastered the clinical subject will exhibit appropriate hand–eye coordination However when the difficulty is increased by telling the child to hurry or by giving him a more complicated puzzle, or by introducing irrelevant stimuli his coordination breaks down. He can no longer move his hands while monitoring them visually His movements become uncoordinated or he gives the impression of working like a blind child

The research team the clinicians and parents noticed that all the children of the clinical group had more difficulty in shifting their point of view or in shifting from one activity to another The parents report that when such a child is taken out of his usual round of activities he gets more restless than normal In therapy when the child with shifting difficulties finds out that his therapist has been changed or that his program has been changed he gets very upset. *Shifting* difficulties are often obvious on problem solving tasks If the child has inserted the wrong piece in a puzzle he has difficulty taking it out just as he has difficulty when a piece should be reversed The SON-subtest of the mosaic problems presents an opportunity to observe shifting problems There a model is presented in a rectangular *position* for the first few tasks then the position changes *into* an angle-position Children of the clinical group have difficulty adjusting to such a positional change However once adjusted, the child may perform correctly again and proceed with the test. Another test requires the child to shift from color sorting to form sorting, a shift which is difficult for the clinical child to perform

Elaborati e performances

The sensory-motor stage of elaborative performances was evaluated by collecting

Table II *General behavior between groups (numbers of subjects and percentages)*
App = appropriate Inapp = inappropriate

	Normal group		Clinical group	
	App	Inapp	App	Inapp
Attention span	(30) 100%	–	–	(30) 100%
Anticipation	(30) 100%	–	–	(30) 100%
Hand-eye coordination	(30) 100%	–	–	(30) 100%
Shifting	(30) 100%	–	–	(30) 100%

Summarizing the results of the input performances reveals some tendencies First there is no input task which appears to separate clearly the normal from the clinical group Most tests give some inappropriate responses in the normal group as well as in the clinical group There are a few normal children whose pure tone thresholds cannot be considered within normal limits Not all normal children have a speech discrimination score of 100% correct Some fail in sequencing tasks of auditory or visual nature In both the normal and the clinical groups more children can not be tested or give inappropriate responses when the performances being tested are more complex

However the incidence of children who can not be tested and of children who give inappropriate responses is higher in the clinical group than in the normal group

A similar finding is observed as the tasks increase in complexity for again the number of children not tested or giving inappropriate responses is greater for the clinical group

A second tendency is also of interest The data for the two groups reveal that an appropriate response on a peripheral task such as pure tone thresholds does not predict an appropriate response for a more complex task There are children who have normal pure tone thresholds who do not score appropriately on speech discrimination Then too there are children who score normally on a dimensional analysis but fail sequencing tasks of the same modality

General behavior

General behavior was evaluated exclusively by observation since no standardized tests could be applied However it was surprising to notice the consistency of the reports of psychologists audiologists therapists and parents when information was compared Table II presents the results of these observational evaluation scores All children were judged Therefore there are no tested or non-tested entries in Table II Every child was evaluated for appropriateness in attention span anticipatory performance hand-eye coordination and shifting behavior If the behavior of a child was judged to be inappropriate it does not mean that the specific performance was totally lacking For example all children of the clinical group were judged inappropriate in attention span This is not to say that they have no attention span but rather that the length of time during which attention is focused upon a stimulus was less stable than normal If a task becomes more difficult attention span of these children decreases more rapidly than normal and they may show signs of panic Therefore attention span depends upon the amount of difficulty which a problem presents A child may perform adequately on a task at his level but if the therapist raises the amount of difficulty his attention span breaks down more rapidly than expected normally Complexity can also be manipulated by increasing the amount of stimuli external to the task The child may be able to focus on a task in a quiet corner with just the relevant material on the table However he may be unable to focus on the same task when sitting in the middle of a room with more irrelevant stimuli around him In the first situation he appears at ease while in the latter he will appear to be hyperactive Such changes of the stability of attention

misunderstanding of the tasks rather than to deficits in problem solving abilities. The non-verbal SON test was standardized on normal hearing children and on deaf children. The pronounced failure of the clinical group for this test may point out that the problems of the clinical group are different from the problems of deaf children. The Borel Maisonny test is a test for young children. All normal children who were tested passed. Their behavior during the testing pointed out that the test did not present problems for them for they solved the tasks easily. However 50% of the clinical cases failed the test. It appears that the test includes items which are difficult for the clinical group tested. However the possibility of mental retardation cannot be ruled out. In order to examine this possibility the linearity of three subtests of the SON battery was examined. If mental retardation were indeed the explanation, then the scores on various subtasks would be consistent and lower than the normal group. However inspection of the data on Table III reveals that more than half of the normal children and 62% of the clinical cases had non-linear profiles. The question of mental retardation remained unresolved.

Clinical observations are recorded last on Table III. All children of the clinical group demonstrated either a consistent non-linearity between operative and figurative performances or presented poorer direct and better deferred imitation. Piaget in a lengthy discussion of the development of operative and figurative performances points out that one can expect a child who has reached a particular level of operative performance will have also developed the *same* level of figurative performance. Thus when a normal child begins to recognize *pictures he* also begins to name them and at the same time starts to imitate a model which is no longer present. By the time a child *begins to* sort objects according to certain qualities or to put them in serial order he begins to draw. This appears to be different in the clinical group. There some children are able to classify or to arrange objects in a series but still cannot recognize pictures or draw. Such non linearity between relatively well developed operative processes and a consistent lag of figurative performance is inappropriate and seems to differentiate part of the clinical group from the normal group. The other part of the clinical group was found to have better performances in deferred imitation than in direct imitation, a relationship which is just the reverse of that found in normal children. As an example of deferred imitation, parents and therapists often report that such a child will produce words spontaneously that he has heard several days previously. If an adult says that word and asks the child to repeat it, requiring direct imitation, the child fails to do so. The observations here point out that this discrepancy indicates a specific difficulty which differentiates some of the clinical group from the normal group.

Speech sound production

Speech sound production was observed by means of a Kay Electric model 6061 B spectrum analyzer with a 6076 scale *magnifier* plug-in unit. A group of 20 normal children were observed but due to shyness in the laboratory *situation only 17 usable sets of* spectrographic recordings were obtained. The 30 children of the clinical group were observed. However only 15 of these children *could produce* speech leaving 15 clinical *subjects* who were not recorded on the *spectrum analyzer*. In addition to the spectrographic recordings a phonemic *analysis* was made of both groups speech sound production. A summary of the results of examination of the speech sound production of the normal and clinical groups of subjects is presented in Table IV.

The first result presented in Table IV, 3000 *Hz*, is an analysis of spectral components at 3000 Hz or above. The presence of high frequency components in this range is *typical*

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Table III *Elaborative performances between groups (numbers of subjects and percentages)*

NT=not tested T=tested App =appropriate Inapp =inappropriate

Normal group		Clinical group			Normal group		Clinical group	
NT	T	NT	T		App	Inapp	App	Inapp
				Sensory-motor/intuit perf				
–	(30) 100%	–	(30) 100%	Imitation	(30) 100%	–	–	(30) 100%
				Figurative				
–	(30) 100%	–	(30) 100%	Language	(30) 100%	–	–	(30) 100%
(9) 30%	(21) 70%	(6) 20%	(24) 80%	Drawing	(21) 100%	–	–	(24) 100%
				Operative				
(7) 23%	(23) 76%	(17) 57%	(13) 43%	Sorting SON	(19) 83%	(4) 17%	(3) 3%	(10) 77%
(23) 76%	(7) 23%	(16) 53	(14) 46%	Borel-Maisonny variables	(7) 100		(7) 50	(7) 50
				Linearity				
(7) 23%	(23) 76%	(17) 57%	(13) 43%	Linearity of SON profile	(11) 48%	(1) 5 %	(5) 38%	(8) 6_%
–	(30) 100%	–	(30) 100%	Linearity between oper./figur perf or better direct imitation and poorer deferred imitation	(30) 100%	–	–	(30) 100%

Standardized scores

information about imitative behavior Since imitation was evaluated by observations and not by tests there are no entries for tested and not tested children As can be seen on Table III all children of the clinical group were judged inappropriate in imitative behavior This result includes not only the imitation of speech in which all children of the clinical group have difficulty but also non verbal activities such as imitation of gestures facial expressions and other activities Difficulties and delay of development of imitation were observed in both direct imitation and in deferred imitation

It was expected that all clinical children would differ in language performances from the normal children since it was for this reason they came to the clinic and were selected as subjects However the same was not anticipated for drawing performance Table III indicates that all normal children were judged appropriate in this respect which means that by the age of five years the normal children had a means of graphic expression This was not the case with the clinical group All of the clinical cases were judged inappropriate This means that the clinical child by the age of five years had not developed any drawing skills

Operative performance was evaluated by means of the SON sorting test or the BM puzzle items SON test scores of the normal children indicate that 17% responded inappropriately However the number of failures was higher in the clinical group where 77% of the tested children did not perform at their age level Upon analysis of the data and discussions with psychologists it became apparent that this high rate of failure in the clinical group was due to

misunderstanding of the tasks rather than to deficits in problem solving abilities. The non-verbal SON test was standardized on normal hearing children and on deaf children. The pronounced failure of the clinical group for this test may point out that the problems of the clinical group are different from the problems of deaf children. The Borel Maisonny test is a test for young children. All normal children who were tested passed. Their behavior during the testing pointed out that the test did not present problems for them, for they solved the tasks easily. However, 50% of the clinical cases failed the test. It appears that the test includes items which are difficult for the clinical group tested. However, the possibility of mental retardation cannot be ruled out. In order to examine this possibility the linearity of three subtests of the SON battery was examined. If mental retardation were indeed the explanation, then the scores on various subtasks would be consistent and lower than the normal group. However inspection of the data on Table III reveals that more than half of the normal children and 62% of the clinical cases had non-linear profiles. The question of mental retardation remained unresolved.

Clinical observations are recorded last on Table III. All children of the clinical group demonstrated either a consistent non-linearity between operative and figurative performances or presented poorer direct and better deferred imitation. Piaget, in a lengthy discussion of the development of operative and figurative performances, points out that one can expect a child who has reached a particular level of operative performance will have also developed the same level of figurative performance. Thus, when a normal child begins to recognize pictures he also begins to name them and, at the same time, starts to imitate a model which is no longer present. By the time a child begins to sort objects according to certain qualities or to put them in serial order he begins to draw. This appears to be different in the clinical group. There some children are able to classify or to arrange objects in a series but still cannot recognize pictures or draw. Such non-linearity between relatively well developed operative processes and a consistent lag of figurative performance is inappropriate and seems to differentiate part of the clinical group from the normal group. The other part of the clinical group was found to have better performances in deferred imitation than in direct imitation, a relationship which is just the reverse of that found in normal children. As an example of deferred imitation, parents and therapists often report that such a child will produce words spontaneously that he has heard several days previously. If an adult says that word and asks the child to repeat it, requiring direct imitation, the child fails to do so. The observations here point out that this discrepancy indicates a specific difficulty which differentiates some of the clinical group from the normal group.

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The first result presented in Table IV, 3000 Hz, is an analysis of spectral components at 3000 Hz or above. The presence of high frequency components in this range is typical

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Table IV *Summary of results for speech sound production for the normal and clinical groups between groups (numbers of subjects and percentages)*

NT = not tested T = tested App = appropriate Inapp = inappropriate

Normal group		Clinical group			Normal group		Clinical group	
NT	T	NT	T		App	Inapp	App	Inapp
(3) 15	(17) 85%	(15) 50	(15) 50	High frequency energy (3 000 Hz)	(17) 100	– –	(5) 33	(10) 67
(3) 15	(17) 85%	(15) 50	(15) 50	Formant clarity	(11) 65	(6) 35	( ) 13	(13) 87%
(3) 15%	(17) 85%	(15) 50	(15) 50	Intonation	(13) 76	(4) 4	(11) 73	(4) 27%
(3) 15	(17) 85	(15) 50	(15) 50	Rate	(17) 100	–	(11) 73	(4) 7%
(3) 15	(17) 85	(15) 50	(15) 50	Consonant clusters	(17) 100		(1) 7	(14) 93

of consonants and may be used as an index of consonant articulation In Table IV it is seen that all of the normal children s speech is marked by the presence of high frequency components This finding may be regarded as confirming the observation that the normal children produced clear consonants The spectrograms of the clinical group on the other hand offered a marked contrast in this respect Here only 33% of the tested children of this group were found to show spectrographic evidence of the high frequency components accompanying consonant production while 67% were deficient in spectral components above 3 000 Hz This finding may be regarded as confirming the clinical observation that consonant articulations of this group are generally less precise and less intelligible

The next spectrographic interpretation concerns the clarity of vowel formants In the normal speech of adult males clear vowels show formants which are distinct and smooth in appearance Reduced contrast of the formants can result from noise in the vocalic segment and is often caused by voice defects It was for this reason that formant clarity was used in this study However the bandwidth (300 Hz) of the Kay analyzing filter is not ideal for higher pitched voices As a result formant clarity is often reduced in the spectrograms of women and children For this reason the observations concerning formant clarity are to be interpreted cautiously In the normal group 65% revealed clear formant structures as opposed to only 13% of the clinical group This observation suggests a higher incidence of voice problems in the clinical group

The third acoustic factor was considered under intonation The magnifying circuit of the Kay equipment was used to make an expanded spectrogram of the lower 2 000 Hz portion of the child s utterance Expanded spectrograms show the individual harmonics of the voice This enables one to determine the intonation contour as the variation in vocal frequency is called Intonation serves as one of the linguistic cues for questions statements and other types of utterances Of the normal group 76% used appropriate intonation contours for the utterances analysed Similar results were obtained for the clinical group Intonation was the speech sound production ability in which the two groups were most alike

The abscissa of a spectrogram is time so that one can measure the duration of the recorded utterance which in turn allows speaking rate to be calculated All of the normal children were found appropriate having an average rate for the two utterances of 3 3 syllables per second and a range from 2 5 to 4 4 syllables

per second The slower rates were produced by the younger subjects These values were regarded as normal for this age group and the type of material spoken Clinically the impression was formed that rates of ? 0 syllables per second or below were too slow while rates of 4.5 syllables per second or faster were regarded as too fast for the utterances studied By this standard 73% of the clinical group was within the normal classification The average was 2.9 ranging from 1 7 to 5.2 syllables per second

The utterances of the two groups of subjects were analysed phonemically Here the major finding occurred on consonant clusters All of the normal children were able to produce the consonant sequences in the utterances adequately However only seven percent of the clinical group could do so The clinical subjects showed a marked tendency to simplify consonant sequences by omitting one or more sounds Thus, the speech of this group tended to consist of consonant vowel sequences

The picture which emerges from the analyses of speech sound production is that the normal group differs *markedly* from the clinical group in consonant articulation. The latter group is less proficient in this respect and markedly deficient in the production of consonant sequences There is some evidence that the clinical group tends to have noise in their vowel productions which would reduce their clarity Both groups are relatively able to use intonation meaningfully

Within groups comparisons

As pointed out in the introduction the clinical group while all language disturbed included some children who appeared to lag in symbolic performance as well as some who did not The clinical group was subdivided into two groups on the basis of symbolic behavior Subgroup A children seemed to have *symbolic function* For example they appeared to recognize pictures and played with dolls and teddy bears On the other hand the children in subgroup B seemed to lag or lack symbolic function for they either did not look at pictures or were several years late in doing so Nor did children in subgroup B play with dolls or stuffed animal toys

These and other impressions led to the second problem of concern in this investigation namely whether the clinical subjects were a homogeneous group or as clinical impression seemed to indicate two different subgroups Then too it was possible that investigation would indicate that the clinical group was completely heterogenous So the two subgroups were studied in detail to determine if there were consistent differences between the two and if there were similarities within each subgroup This investigation proceeded along the same dimensions as used previously in the between groups analysis i.e input general behavior elaborative performance and speech sound production.

The results of input performances are summarized in Table V Overall it can be seen that more of the subgroup B children could not be tested for input performance than children in subgroup A.

Input

With respect to pure-tone thresholds only two subgroup A children could not be tested while five of subgroup B could not In subgroup A of the 11 inappropriate responses seven were from profoundly deaf children and four from children with conductive hearing losses The four inappropriate pure-tone responses in subgroup B were from children with medium or severe losses Consequently pure tone audiometric results are not seen to differentiate the two subgroups None of the subgroup B children could be tested on acoustic dimensional analysis apparently because they failed to learn the responses necessary for this task. Two-thirds of subgroup A could not be tested on dimensional acoustic analysis but this may be attributed to their hearing handicap, Of those who could be tested in subgroup A four

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(3) 15	(17) 85	(15) 50	(15) 50 %	Formant clarity	(11) 65	(6) 35%	( ) 13	(13) 87%
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(3) 15	(17) 85 %	(15) 50	(15) 50 %	Rate	(17) 100	–	(11) 73	(4) 7
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These and other impressions led to the second problem of concern in this investigation namely whether the clinical subjects were a homogeneous group or as clinical impression seemed to indicate two different subgroups Then, too it was possible that investigation would indicate that the clinical group was completely heterogeneous So the two subgroups were studied in detail to determine if there were consistent differences between the two and if there were similarities within each subgroup This investigation proceeded along the same dimensions as used previously in the between groups analysis i e input, general behavior elaborative performance and speech sound production

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Table V *Input within the clinical group (numbers of subjects and percentages)*

NT=not tested T=tested App =appropriate Inapp =inappropriate SON=Snijders-Oomen non-verbal intelligence scale

Group A		Group B			Group A		Group B	
NT	T	NT	T		App	Inapp	App	Inapp
				Audition				
( ) 11%	(16) 89%	(5) 4 %	(7) 58%	Pure tone thresholds	(5) 31%	(11) 69%	(3) 43%	(4) 57%
(1) 67%	(6) 33%	(1) 100%	–	Dimensional analysis of acoustic stimuli	(4) 67%	( ) 33%	–	
(13) 7? %	(5) 28%	(11) 92%	(1) 8%	Speech discrimination	(3) 60%	(?) 40%	–	(1) 100%
				Acoustic sequences				
(11) 61%	(7) 39%	(1) 100%	–	(*a*) comparison of two-element patterns	(?) ?9%	(5) 71%	–	–
(16) 89%	(2) 11%	(12) 100%	–	(*b*) comparison of three-element patterns	(1) 50%	(1) 50%	–	
(17) 94%	(1) 6%	(12) 100%	–	(*c*) comparison of four-element patterns	–	(1) 100%	–	–
				Vision				
–	*(18)* 100%	–	*(1)* 100%	*Visual acuity*	*(18)* 100%	–	(9) 75%	*(3)* ?5%
(9) 50%	(9) 50%	(12) 100%	–	Dimensional analysis of visual stimuli	(6) 67%	(3) 33%	–	–
(5) 28%	(13) 7?%	(10) 83%	(2) 17%	Mosaic SON	(5) 38%	(8) 6 %	–	( ) 100%
				Visual sequences				
(1) 67%	(6) 33%	(1) 100%	–	(*a*) comparison of two-element patterns	(4) 67%	(?) 33%	–	–
(14) 78%	(4) 22%	(12) 100%	–	(*b*) comparison of three-element patterns	(1) ?5%	(3) 75%	–	
(15) 83%	(3) 17%	(1) 100%	–	(*c*) comparison of four-element patterns	(1) 33%	(2) 67%	–	–

Clinical observation

were able to respond appropriately Again there is no basis for differentiating the two subgroups *Roughly the same results were* obtained on speech discrimination tests Tests of acoustic sequences were too difficult for the subgroup B children *as well as for most of* the A children Generally the results indicate that the two subgroups cannot be differentiated on the basis of auditory input

With respect to visual performance all children were observed on acuity with all of the subgroup A children appearing to be appropriate and only three (25%) of the second subgroup inappropriate Again on dimensional analysis a visual performance the children of subgroup B failed to achieve *sufficiently* to be tested while half of the children of subgroup A could be tested Of those tested in subgroup A 67% responded *appropriately On the* visual mosaic task most of the A children could be tested and most of B could not be tested Only 38% of subgroup A *and none of subgroup B per*formed appropriately on this task The visual sequences were too difficult for the children of subgroup B Some of subgroup A children could be tested with fewer children responding appropriately as the

level of difficulty increased In general it must be said that the visual input results like those for audition do not differentiate the two subgroups

General behavior

All children of the clinical group were judged to have an unstable attention span as reported in the between group results However in controlled situations two observations can be made when the complexity of the situation increases such as having a visitor or when making videotapes the attention span of subgroup A is highly affected Both groups are affected by increased difficulties as when a problem increases above their performance level However group A children demonstrate similar fluctuations of attention span if the material is visual or tactile–kinesthetic or both Children of group B are different. Their attention span is by far the best, even stable, with tactile–kinesthetic materials such as jig saw puzzles. For example a subgroup B child can solve jig-saw puzzles. If a piece falls the child can search for it, pick it up and continue the puzzle. Such a performance cannot be observed in children in subgroup A The subgroup A child who picks up a piece will have forgotten where he was with the solution of the problem

The observations of attention span are divided into three parts and may be seen in Table VI The part two a includes observations on a puzzle of the Borel Maisonny Since the Borel Maisonny is designed for younger children it was used with only 7 of subgroup A and 4 of subgroup B Thus older children are listed as not tested in Table VI Only one child of subgroup A performed inappropriately while the other six performed well The overall test scores on the BM demonstrate that the test was very easy As pointed out earlier inappropriateness of attention span does not mean that the child has no attention span. The child can focus if a problem is at his performance level and if the test situation is not distracting. This was the case for the puzzles of the BM battery What is surprising however is that all children of subgroup B gave appropriate responses This is the only item where children of this group were 100% correct on a standardized test. The inference can be made that this material is easy for the group B child.

Observations using non-standardized tactile kinesthetic material with more complex problems show that the difference between the two subgroups is pronounced As can be seen in 2b of Table VI none of the children in subgroup A performed appropriately while all of subgroup B were successful with tactile–kinesthetic problems

Fluctuations in attention span could also be observed during audiometric testing. A lengthy attention span is required to integrate the series of activities required for play audiometry Group A children gave the impression that they are testable appearing to understand that a tactile–kinesthetic response was required when the tone sounded Inspite of this they failed for their attention span seemed to be too short. For example they would hold a toy on the loudspeaker but not wait for the tone putting it down before the stimuli came The children of subgroup B behaved differently They would hold a toy on the loudspeaker for an extended period When the tone was presented the children appeared to hear it, but they were unable to learn that they had to respond by putting the toy down In short children of subgroup A gave the impression that they cannot wait for the tone while children of subgroup B were able to wait but unable to learn that an auditory signal was to trigger a motor response Of the 7 children of group B who could be tested 71% had appropriate waiting behavior Two were marked inappropriate They were the most severely damaged of the tested children It appears then that subgroup B children have other difficulties than subgroup A children

Anticipation performance appeared to differentiate between the clinical and the normal

Table V *Input within the clinical group (numbers of subjects and percentages)*

NT=not tested T=tested App=appropriate Inapp=inappropriate SON=Snijders-Oomen non-verbal Intelligence scale

Group A		Group B			Group A		Group B	
NT	T	NT	T		App	Inapp	App	Inapp
				A dition				
( ) 11%	(16) 89%	(5) 4 %	(7) 58%	Pure-tone thresholds	(5) 31%	(11) 69%	(3) 43%	(4) 57%
(1) 67%	(6) 33%	(1) 100%	–	Dimensional analysis of acoustic stimuli	(4) 67%	( ) 33%	–	–
(13) 72%	(5) 28%	(11) 92%	(1) 8%	Speech discrimination	(3) 60%	( ) 40%	–	(1) 100%
				Acoustic sequence				
(11) 61%	(7) 39%	(1) 100%	–	(*a*) comparison of two-element patterns	( ) 79%	(5) 71%	–	–
(16) 89%	( ) 11%	(1) 100%	–	(*b*) comparison of three-element patterns	(1) 50%	(1) 50%		
(17) 94%	(1) 6%	(1) 100%	–	(*c*) comparison of four-element patterns	–	(1) 100%		
				Vi ion				
–	(18) 100%	–	(1) 100%	Visual acuity	(18) 100%		(9) 75%	(3) 25%
(9) 50%	(9) 50%	(1) 100%	–	Dimensional analysis of visual stimuli	(6) 67%	(3) 33%	–	
(5) 28%	(13) 72%	(10) 83	( ) 17%	Mosaic SON	(5) 38%	(8) 6_%	–	( ) 100%
				Visual sequences				
(1) 67%	(6) 33%	(1) 100		( ) comparison of two-element patterns	(4) 67%	( ) 33%		
(14) 78%	(4) _%	(1) 100%	–	(*b*) comparison of three-element patterns	(1) 25%	(3) 75%		
(15) 83%	(3) 17%	(1) 100%	–	(*c*) comparison of four-element patterns	(1) 33%	( ) 67%		

Clinical observation

were able to respond appropriately Again there is no basis for differentiating the two subgroups Roughly the same results were obtained on speech discrimination tests Tests of acoustic sequences were too difficult for the subgroup B children as well as for most of the A children Generally the results indicate that the two subgroups cannot be differentiated on the basis of auditory input

With respect to visual performance all children were observed on acuity with all of the subgroup A children appearing to be appropriate and only three (25%) of the second subgroup inappropriate Again on dimensional analysis a visual performance the children of subgroup B failed to achieve sufficiently to be tested while half of the children of subgroup A could be tested Of those tested in subgroup A 67% responded appropriately On the visual mosaic task most of the A children could be tested and most of B could not be tested Only 38% of subgroup A and none of subgroup B performed appropriately on this task The visual sequences were too difficult for the children of subgroup B Some of subgroup A children could be tested with fewer children responding appropriately as the

group Clinical observations and parental reports indicated that group A children moved inadequately as soon as a situation became complex For example when they had a complicated jig-saw puzzle and tried to return to a cupboard their movements became inadequate They would stumble and spill the game on the floor When picking up a toy from under the table these children bump their heads Children of subgroup B were not observed to have such difficulties

The next entry in Table VI evaluates the integration of a visual series It was pointed out earlier that children of the clinical group were deviant in anticipatory behavior when tested with the beads-tube task of the BM battery It could be observed however that children of subgroup B can learn visual anticipation in this situation When the children watched the beads being inserted into the tube and appearing again at the lower end they would learn to displace their gaze from the upper to the lower end of the tube thus demonstrating visual anticipation of a visually *perceived* event Howe er they *did* not reach out in anticipation of the beads falling and being picked up Group A children demonstrated difficulty for either anticipation the *visual* or the tactile–kinesthetic type

The next item refers to the play audiometric task. This time the reference is not to waiting behavior but rather to the learning of a tactile–kinesthetic response to an acoustic stimulus to put a toy down when a tone was presented The seven children of group B who could be tested learned the task only after many trials Children of group A did not have this difficulty Their failure of the audiometric task wa due to a difficulty in attention span as discussed previously and not due to the absence of a tactile–kinesthetic response to an acoustic stimulus

Another set of observations also concerns tactile–kinesthetic components but instead of being coupled with an auditory component as in audiometry coupled *with a visual* component The last set o[illegible] n under anticipation in Table VI is concerned with tactile–kinesthetic–visual integration Parents of children in group A often report that they seem to be over-cautious in simple situations like jumping off a wall or in going with somebody they do not know They lose control in complex situations such as crossing a street When there is only one car they can wait But if there is much traffic they appear to lose their heads and panic

Children of group B behave differently They often run away from home Their mothers have to watch the children continually for they climb walls fences and window sills without realizing the risks they take

Group A children present initial stupor They hesitate when they are in a new situation or when they meet somebody new Not so the group B children They don t seem to notice changes They do not scan a new situation and then adapt to it They either do not notice change or they begin to show panic reactions Eye contact breaks down more rapidly in the children of group B than group A One of the most impressive observations is that these children do not look at you as would another child Group A children however do not differ in eye contact from normal children

Another aspect studied was hand–eye coordination Group A children appear to lose hand–eye coordination whenever a problem *or a situation* becomes more complex. Motor skills of the group A child are adequate in *a simple situation* The child may put beads into a bottle with skilled movements But if another stimulus catches his attention his *hand* movements go on but they become inadequate The visual control disappears because the child looks at something dif*ferent. He* will now miss the opening of the bottle and the beads may spill over the table The group A child will hesitate or refuse to climb difficult places The *group* B child behaves differently In the bottle task he may also lose eye–hand control but he will still be able to put beads into the bottle only with slower movements He

Table VI General behavior within the clinical group (numbers of subjects and percentages)

NT=not tested T=tested App =appropriate Inapp =inappropriate

Group A		Group B			Group A		Group B	
NT	T	NT	T		App	Inapp	App	Inapp
				Attention span				
–	(18) 100%	–	(1) 100%	1 Focus on a stimulus over time stimulus unspecified	–	(18) 100%	–	(1) 100%
				Focus on a tactile-kinesthetic stimulus				
(11) 61%	(7) 39%	(8) 67%	(4) 33%	(*a*) puzzle (BM)*	(6) 86%	(1) 14%	(4) 100%	
–	(18) 100%	–	(1) 100%	(*b*) observation	–	(18) 100%	(1) 100%	–
–	(18) 100%	(5) 4 %	(7) 58%	3 Audiometry to attend or wait	(1) 6%	(17) 94 %	(5) 71%	( ) [illegible]9%
				Anticipation				
–	(18) 100%	–	(1) 100%	1 Integration of a series of successive activities	–	(18) 100%	–	(1) 100
–	(18) 100%	–	(1) 100%	To move adequately in a complex situation	–	(18) 100%	(1) 100%	
(9) 50%	(9) 50%	(7) 58 %	(5) 4 %	3 To integrate a visual series (BM–beads–tube)	(4) 44%	(5) 56%	(4) 80%	(1) 20%
–	(18) 100%	(5) 4 %	(7) 58%	4 To integrate a tactile–kinesthetic–auditory series	(18) 100%	–	–	(7) 100%
				5 To integrate a tactile kinesthetic–visual series				
–	(18) 100%	–	(1) 100%	(*a*) sense of caution	(18) 100%		–	(1) 100%
–	(18) 100%	–	(1) 100%	(*b*) initial stupor	(18) 100%	–		(1) 100%
–	(18) 100%	–	(1) 100%	(*c*) eye contact	(17) 94%	(1) 6%		(1) 100%
				Hand-eye-coordination				
–	(18) 100%	–	(1) 100%	1 Visual monitoring of hand or body movement handling objects in task above performance level	–	(18) 100%		(1) 100%
–	(18) 100%		(1) 100%	Complex motor activities climbing running		(18) 100%	(1) 100	
				Shifting				
–	(18) 100%	–	(1) 100%	1 Difficulty in changing point of view of an ongoing activity		(18) 100%		(1) 100%
–	(18) 100%		(1) 100%	2 To be stubborn	–	(18) 100%	(1) 100%	
–	(18) 100%		(1) 100%	3 Stereotype movement	(18) 100%			(1) 100%
	(18) 100%		(1) 100%	4 Compulsive behavior	(18) 100%			(1) 100%

Standardized scores
Play audiometry

group Clinical observations and parental reports indicated that group A children moved inadequately as soon as a situation became complex For example when they had a complicated jig saw puzzle and tried to return to a cupboard their movements became inadequate They would stumble and spill the game on the floor When picking up a toy from under the table these children bump their heads Children of subgroup B were not observed to have such difficulties

The next entry in Table VI evaluates the integration of a visual series It was pointed out earlier that children of the clinical group were deviant in anticipatory behavior when tested with the beads-tube task of the BM battery It could be observed however that children of subgroup B can learn visual anticipation in this situation When the children watched the beads being inserted into the tube and appearing again at the lower end they would learn to displace their gaze from the upper to the lower end of the tube thus demonstrating visual anticipation of a visually perceived event However they did not reach out in anticipation of the beads falling and being picked up Group A children demonstrated difficulty for either anticipation the visual or the tactile–kinesthetic type

The next item refers to the play audiometric task This time the reference is not to waiting behavior but rather to the learning of a tactile–kinesthetic response to an acoustic stimulus to put a toy down when a tone was presented The seven children of group B who could be tested learned the task only after many trials Children of group A did not have this difficulty Their failure of the audiometric task was due to a difficulty in attention span as discussed previously and not due to the absence of a tactile-kinesthetic response to an acoustic stimulus.

Another set of observations also concerns tactile–kinesthetic components but instead of being coupled with an auditory component as in audiometry coupled with a visual component The last set of observations under anticipation in Table VI is concerned with tactile–kinesthetic–visual integration Parents of children in group A often report that they seem to be over-cautious in simple situations like jumping off a wall or in going with somebody they do not know They lose control in complex situations such as crossing a street When there is only one car they can wait. But if there is much traffic they appear to lose their heads and panic

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gives the impression of a blind child proceeding with tactually monitored movements without visual control Parents of subgroup B children report that they are amazed at how their children can climb in difficult places

Another aspect of interest is shifting ability Again differences have been observed between the two subgroups Reports of parents and observations in the clinic point to the group A children as being stubborn They refuse to do something for an extended period They may not speak for hours in a new situation At home parents complain how difficult it is to make them change their minds Not one of the group B children is described as stubborn When they are put into a new situation they may panic They may refuse to do something but it is easy to make them change their minds

Another feature stereotyped movements was observed exclusively in the children of subgroup B and not in children of subgroup A These are children whose hands tremble when they are tense or upset or interested in an event or object Other children spin any object they can find Some will hit their *heads bite their hands or make facial* grimaces Children of group B who have not developed speech produce stereotyped sounds like aiaiai

Another activity perhaps related to stereotyped movements is compulsive behavior Again compulsive behavior is characteristic only of children *belonging to subgroup B and* not belonging to subgroup A Some of subgroup B children collect pens or rubber bands or candles in a compulsive manner They run for these things each time they enter the clinic and know exactly where to find them Other children open and close doors with increasing speed as if in a trance

Elaborative performances

The three stages studied in elaborative performances were divided into substages according to Piaget In the sensory motor period imitative behavior was found to separate the clinical children from the normal children significantly How do the two clinical subgroups differ in this respect?

Modality specific abilities (Table VII) are *thought to be evaluated by the listening behavior of the children* Listening behavior was observed in all children who did not have a profound hearing loss and no difference was found between children of subgroups A and B The same result was found in simple matching problems involving vision Thus modality specific performance does not appear to differentiate the two groups

The next item on Table VII refers to perception in the sense of intermodality performance For example localization was described earlier as being an expression of intermodality development The results show that all of the children of subgroup A have developed such intermodality performance Three of the subgroup B children could not be tested because it was not possible to elicit reliable responses for such performances The nine who were tested failed to present localization responses It seems that the children of group B are *deviant in intermodality development*

The finding of better direct imitation and poorer deferred imitation was mentioned as being normal for direct imitation develops before deferred imitation All children of the clinical group were found to be delayed in imitation This must mean that during the *first 18 months* when a normal child acquires the ability to imitate directly none of the clinical group has done so For some of the group it appears to take several years longer to learn imitative behavior *When this is the* case the difference between the two subgroups becomes apparent When the children of group A begin to show imitation it is at first deferred imitation Direct imitation is learned by these children only after another time lag The children of group B are different showing the normal pattern of direct before delayed imitation Table VII points out that four of the children of group B have imitative

Table VII *Elaborative performance within the clinical group (numbers of subjects and percentages)*

NT = not tested T = tested App = appropriate Inapp = inappropriate

Group A		Group B			Group A		Group B	
NT	T	NT	T		App	Inapp	App	Inapp
				A *Sensory motor/ ... performance*				
(1) 6%	(17) 94%		(12) 100%	1 Modality specific schemes Listening behavior or visual simple matching	(17) 100%	–	(12) 100%	
	(18) 100%	(3) 25%	(9) 75%	Percept processes inter modality performance (Localization)	(18) 100%	–	–	(9) 100%
	(18) 100%	(8) 67%	(4) 33%	3 When imitation present, better direct and poorer deferred		(18) 100%	(4) 100%	–
				B *Figurative performance*				
(5) 28%	(13) 72%	(1) 8%	(11) 92%	1 Drawing	(10) 77%	(3) [illegible]3%		(11) 100%
	(18) 100%		(12) 100%	2 Picture recognition	(18) 100%		(4) 33%	(8) 67%
(11) 61%	(7) 39%	(6) 50%	(6) 50%	3 Symbolic play (a) BM (bowl)	(6) 86%	(1) 14%	(1) 17%	(5) 83%
	(18) 100%		(12) 100%	(b) Observations of symbolic play	(18) 100%			(12) 100%
	(18) 100%		(12) 100%	(c) Speech with meaning	(18) 100%		(4) 33%	(8) 67%
				C *Operative performance*				
(6) 33%	(12) 67%	(10) 83%	(2) 17%	1 Sorting SON [illegible] (geom. forms)	(7) 58%	(5) 42%	(1) 50%	(1) 50%
	(18) 100%		(12) 100%	Linearity between oper and figur developmental levels	(18) 100%			(12) 100%

Standardized scores

performance while the rest of the group could not imitate. The interesting observation however is that the four children of group B who have learned imitative behavior follow the pattern of the normal child. They first begin to imitate directly when the model is present. Only after a time lag do they begin to show deferred imitation.

In Table VII under figurative performance it can be seen that both subgroups were observed on drawing performance. Five children in subgroup A and one child in subgroup B younger than 5 years were not tested. Considering the tested children it seems from Table VII that drawing performance partially differentiates the two groups. All tested subgroup B children performed inappropriately indicating that none of the children of group B utilized graphic means of expression. However 77% of subgroup A children were regarded as appropriate having developed some drawing skills. Three were judged inappropriate. One of these just turned 5 years old the 2 other children scored at a 5 year level on intellectual development. Thus since all children of the clinical group appear to be delayed in

Table VIII Summary of results for speech sound production for the clinical group within the clinical group (numbers of subjects and percentages)

NT=not tested T=tested App =appropriate Inapp =inappropriate

Group A		Group B			Group A		Group B	
NT	T	NT	T		App	Inapp	App	Inapp
(6) 33%	(1) 67%	(9) 75%	(3) 25%	High frequency energy (3 000 Hz +)	(4) 33%	(8) 67%	(1) 33%	( ) 67%
(6) 33%	(1) 67%	(9) 75%	(3) 25%	Formant clarity	( ) 17%	(10) 83%	– –	(3) 100%
(6) 33%	(1) 67%	(9) 75%	(3) 25%	Intonation	(8) 67%	(4) 33%	(3) 100%	–
(6) 33%	(1) 67%	(9) 75%	(3) 5%	Rate	(9) 75%	(3) 25%	( ) 67%	(1) 33%
(6) 33%	(1) 67%	(9) 75%	(3) 25%	Consonant cluster	– –	(1) 100%	(1) 33%	( ) 67%

drawing production it seems reasonable that these three children had not developed drawing skills yet

On picture recognition all subgroup A children appear to extract meaning from pictures while only 33% of subgroup B do so On the Borel Maisonny task used to evaluate symbolic play 86% of the children tested in subgroup A and only 17% (one subject) of subgroup B were scored as appropriate In observations of spontaneous symbolic play activities all of group A and none of group B were rated appropriate Finally the meaningfulness of speech was observed All children in subgroup A produce some sounds with meaning while only 4 of subgroup B can be heard to produce meaning It is of considerable interest to note that these four children were those whose direct-deferred imitation pattern was similar to that of normal children and those who scored appropriate for picture recognition

The final section of Table VII summarizes the results obtained on operative performance The geometric forms subtest of SON battery was used to evaluate visual sorting While 33% of subgroup A could not be tested 83% of subgroup B were unable to be tested However of the children tested roughly half of each group responded appropriately but only 2 children of subgroup B were tested

For the last item the children of group A appear to present an appropriate linearity between operative and figurative development Group B children are inappropriate in this respect They seem to be more developed in operative processes than in figurative performances However this evaluation includes only observations and not standardized procedures

It appears that localization direct versus deferred imitation patterns drawing picture recognition symbolic play and the linearity between operative and figurative development differentiate the two groups

Speech sound production

The observations on speech sound production are summarized in Table VIII In Table VIII it may be seen that 67% or 12 children of the subgroup A children and only 25% of subgroup B children could be tested This result stems from the fact that most of the children in subgroup B could not talk at all Of the children tested in the two clinical subgroups there is no percentage difference between those able to produce high frequency components One third of the tested children in both subgroups could produce clear

However this amounts to only one child in subgroup B

In formant clarity which should reflect normal voice quality none of subgroup B and only two children in subgroup A were found appropriate With respect to intonation 67% of subgroup A and 100% of subgroup B were found appropriate as judged from spectrographic analysis An interesting finding emerged at this point The children in subgroup A who had high frequency components tended not to be appropriate in intonation while children whose intonation was appropriate tend not to have adequate high frequency components above 3 000 Hz In short these children tend to have either clear consonants and poor intonation or poor consonants and good intonation but not both Thus the children in subgroup A appear to be successful in one aspect of speech sound production or another but not at a more complex level of both As with other performances by this group the children appear to experience difficulty with tasks of a more complex level This is not the case however with the 3 children tested in subgroup B Here only one child the most advanced of the subgroup can produce both high frequency components and adequate intonation The other tested appear to be at an earlier level that is able to produce adequate intonation but not yet able to produce clear consonant In normal development of speech sound production intonation is established before clear consonant articulation is achieved (Gleason 1955 Bolinger 1962)

With respect to rate most children tested in both subgroups were adequate As for consonant clusters all productions of the children tested in subgroup A were inappropriate Thus although 33% of those tested in subgroup A could produce clear consonants none of them could produce a successive series of consonants Again one child in subgroup B the most advanced could produce consonant clusters while the other 2 could not The ability to produce consonant clusters is established after consonant articulation with the less proficient stage being marked by consonant–vowel sequences

Additional comment seems useful at this point In subgroup A 1 children were observed and all could be tested In subgroup B 11 children were observed but only 3 had sufficient speech to make spectrographic analysis meaningful Of the remaining 8 none was able to produce speech This is not to say that these 8 children could not produce sound but rather that the sounds they produced were not speech sounds The difference is great. Any audible noise can be called a sound but it is not necessarily a speech sound Speech sounds belong to a particular linguistic system and may occur only in the sequences allowed by the phonological rules of that linguistic system Prolonged observations of these 8 children of subgroup B revealed no such systematic relationship between their noise and a linguistic system One child of the 8 produced no orally emitted sounds at all during the periods of observation Thus on speech sound production children of subgroup B show a dichotomous characteristic not seen in subgroup A The subgroup B children either can produce speech sounds or they can not. If they do the less proficient will be able to produce meaningful intonation while the more proficient can produce consonants consonant clusters and intonation Thus they appear to follow a normal sequence of developmental stages Children in subgroup A will be able to produce speech sounds but will produce either clear consonants or good intonation but not both They appear unable to deal with the increasing complexity of both intonation and consonant articulation or of consonant cluster sequences

Table VIII *Summary of results for speech sound production for the clinical group within the clinical group (numbers of subjects and percentages)*

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Group A		Group B			Group A		Group B	
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(6) 33%	(1) 67%	(9) 75%	(3) 25%	Rate	(9) 75%	(3) 25%	( ) 67%	(1) 33%
(6) 33%	(1) 67%	(9) 75%	(3) 25	Consonant clusters	– –	(1) 100	(1) 33%	( ) 67%

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However this amounts to only one child in subgroup B

In formant clarity which should reflect normal voice quality none of subgroup B and only two children in subgroup A were found appropriate With respect to intonation 67% of subgroup A and 100% of subgroup B were found appropriate as judged from spectrographic analysis An interesting finding emerged at this point The children in subgroup A who had high frequency components tended not to be appropriate in intonation while children whose intonation was appropriate tend not to have adequate high frequency components above 3000 Hz In short these children tend to have either clear consonants and poor intonation or poor consonants and good intonation but not both Thus the children in subgroup A appear to be successful in one aspect of speech sound production or another but not at a more complex level of both. As with other performances by this group the children appear to experience difficulty with tasks of a more complex level This is not the case however with the 3 children tested in subgroup B Here only one child the most advanced of the subgroup can produce both high frequency components and adequate intonation The other 2 tested appear to be at an earlier level that is able to produce adequate intonation but not yet able to produce clear consonants In normal development of speech sound production intonation is established before clear consonant articulation is achieved (Gleason 1955 Bolinger 1962)

With respect to rate most children tested in both subgroups were adequate As for consonant clusters all productions of the children tested in subgroup A were inappropriate Thus although 33% of those tested in subgroup A could produce clear consonants none of them could produce a successive series of consonants. Again one child in subgroup B the most advanced, could produce consonant clusters while the other 2 could not. The ability to produce consonant clusters is established after consonant articulation with the less proficient stage being marked by consonant–vowel sequences

Additional comment seems useful at this point In subgroup A 12 children were observed and all could be tested In subgroup B 11 children were observed but only 3 had sufficient speech to make spectrographic analysis meaningful Of the remaining 8 none was able to produce speech This is not to say that these 8 children could not produce sound but rather that the sounds they produced were not speech sounds The difference is great Any audible noise can be called a sound but it is not necessarily a speech sound *Speech* sounds belong to a particular linguistic system and may occur only in the sequences allowed by the phonological rules of that linguistic system Prolonged observations of these 8 children of subgroup B revealed no such systematic relationship between their noise and a linguistic system One child of the 8 produced no orally emitted sounds at all during the periods of observation Thus on speech sound production children of subgroup B show a dichotomous characteristic not seen in subgroup A. The subgroup B children either can produce speech sounds or they can not. If they do the less proficient will be able to produce meaningful intonation while the more proficient can produce consonants consonant clusters and intonation Thus they appear to follow a normal sequence of developmental stages Children in subgroup A will be able to produce speech sounds but will produce either clear consonants or good intonation but not both They appear unable to deal with the increasing complexity of both intonation and consonant articulation or of consonant cluster sequences

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The *Between Groups* results indicate that the normal and clinical groups could not be differentiated on the basis of input functions like auditory and visual thresholds and auditory and visual analyses of dimensions and sequences Inappropriate and appropriate responses were obtained from both groups As might be anticipated more children in the clinical group were deficient in input functions In addition more members of the clinical group could not be tested on some input tasks a finding which points to the need of more adequate testing procedures for non verbal children

Several aspects of general behavior appeared to differentiate the two groups The clinical group exhibited greater fluctuation in attention span and poorer hand–eye coordination on the more complex tasks or in the more difficult situations than did the normal children In addition the clinical group had greater difficulty than the normal in anticipation and shifting behavior

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The Within Group results like those obtained in the between groups comparison indicate that input functions do not discriminate among the members of the clinical group However several aspects of general behavior were found to differentiate the two clinical subgroups One discriminating function was attention span Observations of the length of attention span in relation to the type of material used in testing revealed that subgroup B had a better attention span in both simple and complex tasks when the materials required only tactile–kinesthetic manipulation However if the task involved more than one modality as when an auditory or visual component was added these children experienced difficulty Their failure was due apparently to the problem created by the involvement of more than one modality Children of subgroup A on the other hand had difficulty when the situation or task became complex They did not appear to depend on the number of modalities utilized

Another discriminating function was anticipation which yielded results similar to attention span All clinical children had difficulties waiting for events to come Children of subgroup A anticipated adequately n simple tasks but started to have difficulties when the degree of complexity was increased such as when transporting easily-disassembled puzzles from one location to another Subgroup B children were less affected by complexity than subgroup A children but failed when anticipation involved more than one modality For example these children could anticipate visually when the task was primarily visual as in the beads-tube task of the BM-test. They failed to build up anticipatory responses when the task required a kinesthetic–visual integration such as producing tactile–kinesthetic movements when seeing a dangerous dog, or when facing a new situation or a new person. These children also presented poor eye-contact, a performance which includes more than one modality Hand–eye coordination or body–eye coordination was judged inappropriate in all clinical children. However a thorough analysis of the performances of the subgroups in different tasks involving such coordination appears to separate them. Subgroup A children have appropriate hand–eye–coordination in simple tasks They lose coordination as soon as the tasks become more difficult. This observation can be made in any task involving hand–eye coordination by handling objects or performing motor activites The subgroup B children do not seem to depend on such a complexity factor They appear to depend more on the type of task. For example they cannot monitor visually objects as parts of a difficult task like a jig-saw board whose problem is above the performance limits of the child However they are very skilled in complex movements like climbing fences trees The suggestion is made that in the jig-saw task more than one modality is involved the visual and the tactile ones but not so in climbing. Climbing can be done by tactile contact with the object to climb Besides attention span anticipatory behavior and hand–eye coordination shifting performances appear to separate the two groups Clinical and parental reports point to subgroup A children as being stubborn but not the subgroup B children. Subgroup B children may panic in new situations or refuse a task. But it appears to be easy to change their minds. However subgroup B children present stereotype movements like biting their hands spinning objects In addition they present compulsive behavior like collecting pens rubber bands Subgroup A children do not produce such stereotype movements

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one modality These findings support the tentative conclusion that subgroup A children have a disturbance in the integration of successive stimuli when a critical level is exceeded and that subgroup B children have a disturbance in the integration of several sensory modalities

Turning now to the results of this study concerning elaborative function group A children appear to have developed intermodality coordination but have failed on the next level that of direct imitation Inasmuch as Piaget has indicated that success of direct imitation involves not only integration of visual-tactile-kinesthetic or auditory-tactile-kinesthetic modalities but also sequential integration of successive stimuli the tentative conclusion may be advanced that group A children fail direct imitation because they cannot integrate successive stimuli in time Inasmuch as most of the children of subgroup B do not develop imitation their problem seems to be due to a failure in the development of the required intermodality coordination. Once this coordination is developed the child will proceed in the normal sequence of direct imitation followed by deferred imitation.

In regard to figurative processes subgroup B children are found to lag in symbolic development It may be inferred that this failure is due to lack of development of intermodality coordination characteristic of a lower level of development This supports the tentative conclusion that intermodality coordination is a prerequisite for symbolic function Subgroup A children have developed intermodality processes and symbolic function which allows the tentative conclusion that sequential integration is not a prerequisite for symbolic function Inasmuch as subgroup A children have difficulties in figurative performances such as drawing and speaking it would seem to support the tentative conclusion that these activities require an extensive degree of sequential integration

Finally speech sound analysis of the children of subgroup B revealed that eight of these children failed to produce speech sounds These same children failed figurative performances completely such as picture recognition symbolic play imitation drawing Only four of group B children produce speech These children do localize recognize pictures imitate directly Their imitation follows a normal sequence first direct imitation Their speech sound production also follows a normal sequence 3 of the children have correct intonation but not correct consonants Only one the least damaged child of group B has both correct intonation and correct consonants It seems therefore that once a critical amount of intermodality schemes have developed the child of group B will begin to imitate will then develop symbolic processes and learn to produce speech sounds in a normal sequence The speech sound analysis of the subgroup A children also supports the findings of general and elaborative behavior They either can produce intonation correctly or the consonants but not both This seems to support the complexity dependency of these children They appear to integrate only a reduced amount of stimuli at a time and thus fail to control a critical amount of sequential stimuli.

In summary the clinical group of severely language handicapped children of this study presents two subgroups of children The primary difficulty of subgroup A children appears to include a level of sequential integration The subgroup B children appear to have difficulty on an intermodality level of perception which seems to develop primary to symbolic and language acquisition The hypothesis can be advanced that a critical amount of intermodality connection is necessary for imitation for symbolic processes and for language acquisition A critical amount of sequential integration is a prerequisite for direct imitation and speech sound production.

ing the results obtained on input performances which are of a modality specific kind too The differences are found in more complex perceptual activities Most of the subgroup B children failed intermodality tasks such as localizing an acoustic signal Only the least damaged of the subgroup B children four subjects presented localization behavior All children of subgroup A presented appropriate intermodality performances However subgroup A children were inappropriate in the relationship between direct and deferred imitation Normal children and children of subgroup B who had developed imitation show better performance in direct imitation than in deferred imitation None of the subgroup A children present this type of relationship During the time the normal child acquires direct imitation subgroup A children appear to lack such behavior By the time the normal child develops deferred imitation the subgroup A child also begins to develop deferred imitation but will still lack direct imitation *Figurative performances strongly differentiate* the two subgroups All clinical children are delayed in drawing performances However subgroup A children appear to learn to draw after a delay They recognize pictures and play *symbolically Subgroup B* children are different None of them had any graphic means of expression They all lack symbolic play Only four of the subgroup B children recognize pictures and produce speech sounds with meaning

A comparison between operative processes and figurative processes indicates that subgroup A children seem to develop both types of processes in a linear relationship Subgroup B children are different They lag or even lack completely figurative processes but not operative processes Their operative performances present a higher level of development than figurative processes This corroborates the clinical impressions of a lag of symbolic performances in the clinical subgroup B

In regard to speech sound production all children of subgroup A had this ability but only *four of the subgroup B children* However productions of subgroup A were characterized by an either–or aspect of being able to produce consonants or to produce intonation but not both simultaneously In *distinction the four subgroup B children* who had speech sounds first have intonation while the most advanced has both intonation and consonants This is the normal sequence of acquisition

Conclusion

From the results of this study it appears that severely speech and language handicapped children can *be distinguished from normal* children not only on the basis of their language difficulties *but also on the basis of their* general behavior elaborative function and speech sound production The differences *point to a disturbance primary to language* acquisition affecting sensory-motor performances in Piaget s meaning Modality specific input functions were not found to be an adequate basis upon which to distinguish the clinical from the normal group

The severely speech and language handicapped children studied here were not a homogeneous group but were found to represent two subgroups which differ in several respects

In general behavior it was found that subgroup A children fail when tasks involve a critical degree of complexity Subgroup B children fail when tasks involve more than

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Otosclerosis in Norway

A Geographical and Genetical Study

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Otosclerosis in Norway

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JENS G. HALL

From the Department of Otolaryngology
Rikshospitalet, Oslo, Norway

UPPSALA 1974

Introduction

Today one may with a high degree of accuracy maintain that the efforts of the ear nose-throat surgeons have solved the problem of the surgical treatment of otosclerosis (Chevance et al 1970) This assertion provides a good picture of the gap which exists between the surgeons successes and our biological understanding of the disease Why is it so rare among the Japanese and the Orientals while being frequent among members of the Caucasian and American-Indian races? (Sakai 1971) Why are there so many otosclerotic foci in a random histological material while so few get clinical symptoms of this disease? (Engström 1939) The works of Engström from 1939 and 1940 raised questions which are still of current interest but which cannot be answered until as a background we have available epidemiological studies of the distribution of the disease in countries where medical treatment is so readily available that reliable statistics can be derived because we may expect most individuals with clinical symptoms to undergo medical examination Larsson (1960) states

In view of the effective surgical methods of treatment now adopted most otosclerosis patients will sooner or later seek medical advice because of reduced hearing. As shown later this may not be quite true In countries such as the Scandinavian where the ear nose and throat departments have every technical facility to diagnose the disease one might expect that these patients would always be directed to a hospital where the efficacy of surgical treatment can be estimated Concerning Norway this expectation may also not hold true

The purpose of this study is to consider the geographical distribution and the possible inherited tendency of otosclerosis in Norway and to provide a survey of the number of Norwegians suffering from otosclerosis in this country

Studies of similar character are not numerous The above mentioned paper of Larsson is a genetic study of the occurrence of the disease in the families of 762 otosclerosis patients and it may serve as a model for similar heredity studies Larsson did not aim at giving a survey of the geographical distribution of otosclerosis in Sweden Among his findings one might emphasize the fact that there were twice as many women as men among the probands whereas among their closest relatives i.e. parents brothers and sisters of the patients 8 6 per cent were men and 11.5 per cent women, thus a much smaller and not statistically significant predominance of women Larsson states that 80 per cent of the patients information about otosclerosis within the family were true Furthermore he stated that most of the cases which *came to treatment* were between 11 and 42 years of age

Shambaugh Jr described in 1949 his experience from 2 100 patients who had been operated by the "old" method fenestration He indicated that the disease strikes 0.5 to 1 per cent of the white population, that the loss of hearing normally starts about the age of 20 and only in rare cases during childhood and that the ratio of women to men is 3 2

Ballantyne in his book Deafness (1960) sums up the general facts about otosclerosis now accepted in most textbooks The loss of hearing is usually noticed during the teens or early twenties and twice as often among females than among males In half of the cases also another member of the family suffers from a similar loss of hearing, and usually the

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hearing loss in women seems to be aggravated during pregnancy No one knows the cause of this If the disease makes its debut during pregnancy it may be attributable to some hormonal cause while its familial occurrence indicates hereditary factors

Altman et al (1967) gives a survey of the histological material of otosclerosis until 1967 A total of 4 662 patients with otosclerosis are involved From this material we draw the following conclusions Otosclerosis is a hereditary disease frequent among Caucasians (whites and East Indians) but very rare among negroes and people of Mongolian descent (Japanese Indonesians Chinese American Indians) This distribution may suggest that the disease originally started through a genetical mutation The fact that it is so rare among Mongols and so frequent among Americans but not among American Negroes may be due to the fact that there has not been much interbreeding between these races The dominance among women is difficult to explain Moreover the authors emphasize their lack of reliable data concerning the distribution of otosclerosis in different races particularly among negroes living in the U S Therefore their assertions are under correction The authors state that in autopsies from the white population otosclerosis is found histologically in 8 3 per cent while only 0 99 per cent have stapes fixation In both cases the ratio of women to men is like 7 6 Among Negroes in the U S particularly in New York otosclerosis seems histologically to be seven times rarer than among whites but the authors consider the sample of Negroes examined previous to 1967 as too small and also the low number of clinically diagnosed otosclerosis in negroes may be due to their general lack of access to medical service

Davis & Silverman (1970) in their book Hearing and Deafness present the data on otosclerosis which by then were commonly accepted Otosclerosis causes stapes fixation and loss of hearing only in approximately 10 per cent of those cases in which it occurs histologically The hereditary factor exists in all persons with histological otosclerosis but those who manifest clinical symptoms are the least fortunate ones in a much larger group of carriers of the gene This may explain why loss of hearing may not occur in one or more generations of a family with this inherited tendency despite the fact that the disease usually is considered as autosomal dominant hereditary without complete manifestations

Sakai (1971) states from Japan that until December 1971 he had seen only 197 cases of otosclerosis in the otological department of Keio University There was no significant difference between men and women and progressive loss of hearing among family members was found only in 20 per cent of the cases

Morrison (1967) examines the literature on otosclerosis from 1938 and onwards concluding as follows Otosclerosis is a disease that occurs only in man and principally among people of Caucasian descent It is a very frequent cause of deafness in Europe Balkan Middle East and India and among the whites of North- and South America Australia New Zealand and South Africa It occurs also in Malaya New Guinea the Philippines and in Japan then among people of mixed race of Mongolians Negroes and Ainu (people from Hokkaido the Kurils Sakkalin) It is rarely seen among pure Mongols and Negroes It is found among the Negro population of America and the West Indies although ten times as rarely there as among people of the Caucasian race Morrison obtains his data on otosclerosis from a study of 150 probands and their families and arrives at the following conclusions Clinical otosclerosis occurs in 0 3 per cent of the population in England in 91 per cent of the cases it starts between 15 and 45 years of age in 2 per cent under 10 years in 3 per cent between 10 and 15 years and in 4 per cent above 45 years This age distribution is identical for both men and women The author also discusses the widespread opinion that the disease is twice as frequent among women as among men believing that

this assumption does not stand up to closer examination In the first place there are more women than men in the populations which have been studied and women are also more inclined to consult a doctor Secondly unilateral otosclerosis and asymmetric deafness is much more frequent among men (70 per cent as compared to 9) Thirdly the attention of men is not so easily attracted to their disease as they are living and working in more noisy conditions They may have a neurogenic loss of hearing concealing a possible otosclerosis Fourthly the hormonal influence during pregnancy may tend to increase the hearing loss in women Concerning this last assumption, Morrison states that in 12 per cent of all women suffering from otosclerosis the hearing loss was the first symptom to be discovered and in a further 47 per cent the loss was aggravated during pregnancy The reason may be the osteoporosis occurring during pregnancy and lactation The heredity seems to be dominant in some families where it follows the Mendelian laws In other families with this inherited tendency however otosclerosis occurs only in 10 per cent of the expected number because some family members merely become carriers of the disease and do not show its clinical manifestations. These may however transfer clinically manifest otosclerosis to the next generation

Many authors (e g Morrison 1967 Morrison & Bundley 1970) discuss the question of whether there is a common cause in both osteogenesis imperfecta (van der Hoeve de Kleyn s syndrome) and otosclerosis They conclude that there is no proof that these diseases are due to the same anomalous mutation, but they belong to the same family of inherited collagen anomalies The deafness caused by osteogeneus imperfecta is described as a genocopy of otosclerosis" In Norway too this question has been a subject of interest Opheim described in 1968 five operated cases Hall & Röhrt (1968) *studied the stapes* histologically in one case and so did Hall & Lexow in 1973 (in preparation) In these studies the histological findings were *very similar in the two diseases but the* fragile fibrous stapes crurae seen in *osteogenesis imperfecta* were not like the otosclerotic ones

Material

The records of patients with the clinical diagnosis otosclerosis during the decade 1960–1969 were examined In this period otosclerosis operations were performed in the E N T departments of Rikshospitalet and Ullevål Sykehus, Oslo and in the cities Bergen Namsos Bodø and Tromsø Initially an *inquiry* was sent to the remaining E N T -*departments* in the country They all stated that every case of otosclerosis had been referred to one of the above mentioned clinics A study of otosclerosis among the Lapp population was also planned but it became apparent that *this* would require a separate study including a family anamnesis *and an* audiometrical study of a substantial number *of Lapps* Practical *difficulties led to* temporary postponement of such a study as the Lapps do not join in great numbers except when gathering their reindeer *for slaughtering*, a time when one cannot expect them to participate in anything *else*. However it was confirmed that otosclerosis exists among Lapps (see the discussion)

The information obtained from the files was recorded on a form containing columns for sex age familial inheritance therapeutic measures, place of birth and residence (*Fig. 1*) One form was filled out for each patient, *2066* persons in all on the basis of the records from the *departments in* question during the decade 1960–1969 This period gave no correct impression of *the total* capacity of the

hearing loss in women seems to be aggravated during pregnancy No one knows the cause of this If the disease makes its debut during pregnancy it may be attributable to some hormonal cause while its familial occurrence indicates hereditary factors

Altman et al (1967) gives a survey of the histological material of otosclerosis until 1967 A total of 4 662 patients with otosclerosis are involved From this material we draw the following conclusions Otosclerosis is a hereditary disease frequent among Caucasians (whites and East Indians) but very rare among negroes and people of Mongolian descent (Japanese Indonesians Chinese American Indians) This distribution may suggest that the disease originally started through a genetical mutation The fact that it is so rare among Mongols and so frequent among Americans but not among American Negroes may be due to the fact that there has not been much interbreeding between these races The dominance among women is difficult to explain Moreover the authors emphasize their lack of reliable data concerning the distribution of otosclerosis in different races particularly among negroes living in the U S Therefore their assertions are under correction The authors state that in autopsies from the white population otosclerosis is found histologically in 8 3 per cent while only 0 99 per cent have stapes fixation In both cases the ratio of women to men is like 7 6 Among Negroes in the U S particularly in New York otosclerosis seems histologically to be seven times rarer than among whites but the authors consider the sample of Negroes examined previous to 1967 as too small and also the low number of clinically diagnosed otosclerosis in negroes may be due to their general lack of access to medical service

Davis & Silverman (1970) in their book Hearing and Deafness present the data on otosclerosis which by then were commonly accepted Otosclerosis causes stapes fixation and loss of hearing only in approximately 10 per cent of those cases in which it occurs histologically The hereditary factor exists in all persons with histological otosclerosis but those who manifest clinical symptoms are the least fortunate ones in a much larger group of carriers of the gene This may explain why loss of hearing may not occur in one or more generations of a family with this inherited tendency despite the fact that the disease usually is considered as autosomal dominant hereditary without complete manifestations

Sakai (1971) states from Japan that until December 1971 he had seen only 197 cases of otosclerosis in the otological department of Keio University There was no significant difference between men and women and progressive loss of hearing among family members was found only in 20 per cent of the cases

Morrison (1967) examines the literature on otosclerosis from 1938 and onwards concluding as follows Otosclerosis is a disease that occurs only in man and principally among people of Caucasian descent It is a very frequent cause of deafness in Europe Balkan Middle East and India and among the whites of North and South America Australia New Zealand and South Africa It occurs also in Malaya New Guinea the Philippines and in Japan then among people of mixed race of Mongolians Negroes and Ainu (people from Hokkaido the Kurils Sakkalin) It is rarely seen among pure Mongols and Negroes It is found among the Negro population of America and the West Indies although ten times as rarely there as among people of the Caucasian race Morrison obtains his data on otosclerosis from a study of 150 probands and their families and arrives at the following conclusions Clinical otosclerosis occurs in 0 3 per cent of the population in England in 91 per cent of the cases it starts between 15 and 45 years of age in 2 per cent under 10 years in 3 per cent between 10 and 15 years and in 4 per cent above 45 years This age distribution is identical for both men and women The author also discusses the widespread opinion that the disease is twice as frequent among women as among men believing that

Results

Distribution of the material according to sex and county

Fig 3 gives a survey of the number of patients with the diagnosis otosclerosis derived from the respective departments It also shows the ratio of men to women Rikshospitalet had the greatest number of patients 693 followed by Bergen with 597 It appears from the tables that the figures are somewhat fluctuating During the years 1963–1967 the number of cases was high in all departments This circum stance will be discussed later The proportion of men to women at Rikshospitalet and in Bergen was approximately 3 5 at Ullevål 1 2, in Namsos 2 3 in Bodø 3 4 and in Tromsø 1 1 The average proportion of men to women is 3 Fig 4 shows the distribution of cases in our different counties in proportion to their population The population numbers obtained from the Central Bureau of Statistics are from the year 1965 which is the middle of the period concerned

Fig 4 The number of cases seen in proportion to the total population gives the frequency with each county

Geographical distribution

Data on place of birth and residence (Fig 5) and on the patients shift of residence, were taken from the cover of the records A total of 822 or approximately 40 per cent had moved from their birth-place However the distribution of the disease according to coun ties and geographical position turned out to be identical whether one calculated according to their place of birth or their residence as shown in Fig. 5 This point was statistically verified by taking the addresses of 50 patients who had moved and distributing these to the counties representing their new residen e No statistically significant difference emerged in the distribution of patients in the various counties Most moves are intra-county and not inter-county

Fig 3

Fig 5

2* 740830

Fig 1

various departments because otosclerosis surgery was not performed before 1961 in Bergen and not before 1967 in Tromsø However the distribution seen on a national scale was probably not affected by this as the patients from these departments were previously directed elsewhere They have therefore been recorded as belonging to the department into which they were admitted

The data processing procedure

The data from each form were later punched on cards after the elaboration of card headings and flow-charts By means of flow-charts one may find out which classifications must be performed before the different data within each group can be listed one by one and in combinations Then a program for the machine must be made Starting from the collected data and the questions one wants answered a macro flowchart is designed which broadly outlines those operations and calculations the computer has to carry out to give the wanted information from the material On the basis of this a micro flow-chart is designed which in detail tells the computer each single step to be performed while carrying out the different calculations In this case these consisted of accumulations of and tests on the different criteria These were then translated to a Fortran code (i e a language understandable by the computer) and punched

The program was first tested in the computer with a limited number of cards The result was controlled by hand to see if it was in accordance with the answers wanted from the different criteria The questions asked to the computer are shown in Fig 2 The results appear on data lists they are transferred to forms as shown in the figures seen later

Fig 2

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Fig 2

[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	1.	3.4	17 5	[illegible]	25.3	[illegible]
[illegible]	[illegible]		2	17.4	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	5		17 2	27 1	27.4	25.3
[illegible]	[illegible]	[illegible]	2	[illegible]	22 1	32	31.3
[illegible]	[illegible]	1			[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	5

Fig 8

The two maps of Southern and Northern Norway (Figs 6 and 7) clearly reflect the fact that the number of cases is proportionate to the density of population The somewhat uneven distribution in densely populated areas will be discussed later

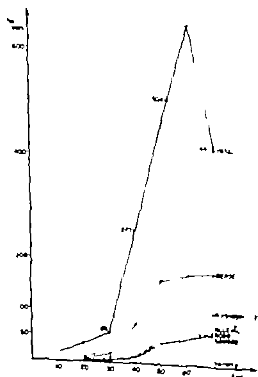


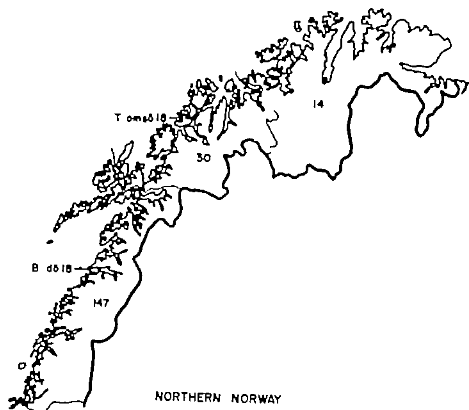
Fig 9

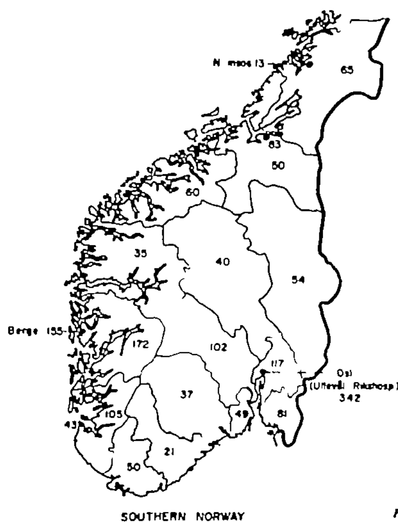
Age distribution

The age distribution appears from Figs 8 and 9 The greatest number of patients were within the group 50–59 years totalling 714 cases or 35 per cent. Furthermore one notes that 477 cases or 23 per cent were older than 60 years and 31 or 1.5 per cent younger than 20 Besides it is remarkable that at Rikshospitalet the largest group was the one between 40 and 49 years whereas the greatest number of patients both in Bergen and Tromsø were older than 60 The reason an accumulation of patients in certain districts will be discussed later The age distribution is also shown in a diagram (Fig. 9) in order to facilitate a general survey

Heredity

The concept of familial occurrence in otosclerosis is well accepted among otologists and further confirmed by the records investigated in the present study If no other member of the family had this disease this point was al





Figs 6 and 7. Geographical distribution of cases

[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]					[illegible]	
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]			[illegible]	
[illegible]	[illegible]	[illegible]			[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

Fig 12

A survey of the hearing loss reported within the families is given in Fig 12. This table must be read crosswise vertically/horizontally e.g. how many patients stated that their grandparents and/or more far-off relatives had a reduced hearing is shown in the top right hand corner

Operations

It was not the purpose of this study to state the results or the achieved improvement in hearing after surgery However it was of interest to compare the number of operations performed to the number of diagnosed clinical otoscleroses To a certain extent such a survey (Fig 13) reveals how adequate Norwegian otologists find the present surgical technique. The figure gives an idea of the difference in opinion as to the selection of patients for operation, and about the indications for operation maintained in the various departments These questions will be discussed later

It was also interesting to see how many patients had been operated *bilaterally* and how many had been operated by the old method fenestration which is today considered out moded Fig 14 shows all the operations performed on the patients including those before 1960 1388 patients were operated once 137 were operated more than once on the same side usually a stapediolysis the first time and a stapedectomy secondly or a reoperation *either to correct the position of the prosthesis* or to renew it. 435 were operated bilaterally Among these 148 came from Rikshospitalet

[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			[illegible]		[illegible]	
[illegible]						
[illegible]				[illegible]		

Fig 13

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]		[illegible]		[illegible]
[illegible]	[illegible]				[illegible]
[illegible]	[illegible]		[illegible]		[illegible]
[illegible]	[illegible]				[illegible]
[illegible]	[illegible]				[illegible]
[illegible]					
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

Fig 14

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Fig 10

ways marked in the files Fig 10 shows that 51 per cent of the patients had relatives with reduced hearing and 1017 or 49 per cent did not However by comparing the results from the various departments with each other it was revealed that the extent to which the patients were questioned was not the same in all hospitals For instance among the patients at Ullevål 80 3 per cent reported the presence of family members with a hearing loss whereas in Tromso only 32 per cent This may be a true difference or the result of inadequate questioning in the latter hospital Fig. 11 shows the distribution of hearing loss among parents grandparents siblings and more remote relatives Among the total of 2066 persons 113 stated that one of their grandparents had a reduced hearing It may be deduced (see Discussion) that 0 3 per cent of the Norwegian population have otosclerosis whereas the corresponding figure for the patients grandparents is 1 4 per cent 515 of the 2066 patients stated that one of their parents also suffered from reduced hearing which represents 12 5 per cent Thus considerably higher figures are found for the relatives of otosclerotics than among the rest of the population Unfortunately it was impossible to calculate corresponding figures for siblings as the records did not tell how many brothers and sisters there were However if one considers hypothetically the possibility that they had one two or three brothers or sisters of whom one was suffering from a hearing loss the figures can be calculated to 13 2 4 4 and 3 3 per cent respectively If they had two or three brothers or sisters and two or more of these also were suffering from hearing loss the figures would be 2 5 and 1 9 per cent respectively which proves that also among brothers and sisters hearing loss is considerably more frequent than among the rest of the population (0 3%)

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			[illegible]	[illegible]	
[illegible]	[illegible]		[illegible]			[illegible]
[illegible]	[illegible]				[illegible]	
[illegible]				[illegible]	[illegible]	
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Fig 11

[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
					[illegible]
[illegible]	[illegible]				
[illegible]	[illegible]	[illegible]			[illegible]
[illegible]	[illegible]	[illegible]			[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			[illegible]		[illegible]	[illegible]
[illegible]						
[illegible] [illegible]				[illegible]		

Fig 13

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]		[illegible]		[illegible]
[illegible]	[illegible]				[illegible]
[illegible]	[illegible]		[illegible]		[illegible]
[illegible]	[illegible]				[illegible]
[illegible]	[illegible]				[illegible]
[illegible]					
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

Fig 14

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	TOTAL
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HARD OF HEARING IN THE FAMILY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] HARD OF HEARING IN THE FAMILY	[illegible]	[illegible]	[illegible]	[illegible]	110	[illegible]	[illegible]

Fig 10

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CLINIC	NO HARD OF HEARING	GRAND PAR.	PARENTS	[illegible]	MORE THAN [illegible]	[illegible]
[illegible]	[illegible]			[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
TOTAL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Fig 11

Discussion

General remarks

The primary object of this study was to provide a survey of the geographical distribution of otosclerosis in Norway. As this approach involved the necessity of examining the records of every single patient, the task was enlarged so as to include also the distribution according to sex and age, familial hardness of hearing, operations and the distribution of hearing aids. However, it must be pointed out that several reservations must be applied to a study of this kind.

As for the geographical distribution, we have found no comparable figures from other countries, since other studies have concentrated mainly on histological problems (Engström 1939), genetic ones (Larsson 1960) or racial aspects (Altmann et al. 1967, Morrison, 1971). As stated in the section "Material", we originally planned to include a statistical survey of otosclerosis among the Lapps. This question was discussed with the otologist in Tromsø (I. Mair) who had previously contacted the chief physicians of Luleå and Oulu, the northern districts in Sweden and Finland with a Lapp population. None had seen otosclerosis in Lapps. However, at Rikshospitalet a 40-year-old reindeer-owner was operated on by O. Opheim in 1956. At the Bodø clinic A. Gulsvik performed one operation in 1968, and in 1971 I. Mair also performed a stapedectomy on a Lapp, and had the foot plate histologically examined. These three cases prove that otosclerosis also occurs in Lapps.

Concerning the data on the number of patients, geographical, sex and age distribution, hearing aids, noise exposition and the influence of pregnancy, it is assumed that the presented data are reliable and complete. As for the familial occurrence one had to rely upon the patients' own report of their family members' state of hearing, and such statements are subject to inaccuracies.

Another objection to this study is that it hardly comprises all cases in this country, only those who have been seen and diagnosed by a doctor. Of course, there are some patients suffering from otosclerosis who never become hospitalized, e.g. because they have another and more serious disease which prevents them from undergoing surgery, or they do not consult a doctor because they do not know or believe that anything can be done for them. They may have a long distance to the doctor, fear of operations, or they have never heard about the possibility of any therapy. This point is further discussed under "Geographical distribution".

Information on these three cases is based on personal communication between the author and the surgeons involved.

Numerical distribution

During the period 1960–1969, a total of 2066 cases of otosclerosis were seen in Norway (Fig. 4). This represents 0.56 per thousand of the population. The present study, however, only comprises a 10-year period. Assuming that otosclerosis for the major part occurs within a 50-year period of life, on the average otosclerosis in Norway occurs in 0.3 per cent of the population. It is hard to find comparable figures from other countries. Shambaugh (1949) states that otosclerosis possibly affects 0.5–1 per cent of the white population, but adds that no authors give any exact statistics of the incidence. However, Morrison & Bundey (1967) reported a major genetic and clinical study undertaken in East London during the years 1961–1964. Among a population of 248591, 76 patients were discovered with otosclerosis, from which the prevalence in East London was calculated to be 0.3 per cent, or the same as in Norway.

Sex distribution

In this study the proportion of women to men is 3:2. As mentioned before, this point has

NO OF OPERATIONS PERFORMED [illegible] EACH CASE

	ONE SIDE	ONE SIDE TWICE OR MORE	BILATERAL	FENESTRATION
ONE SIDE	1295		56	54
ONE SIDE TWICE OR MORE		111	18	25
BILATERAL	FENESTRATION	FE STRATION 1	9	22
FENESTRATION		1		19

Fig 15

which corresponds to 21 per cent of that de partment s cases 180 from Bergen which is 30 per cent of their cases and 105 from other clinics In all 168 fenestrations were perform ed or 1 8 per cent of the total material Fig 15 shows the combinations of operations applied seen on a national scale Like Fig 12 this figure must also be read crosswise

Special circumstances

Special circumstances are usually noted among the routine anamnestic information in the re cords These data are shown in Fig 16 where the first column refers to the use of hearing aids In all 759 of the 2066 patients were or had been using hearing aids which represents 37 per cent The distribution of those em ploying hearing aids varied somewhat when seen in proportion to the number of patients in the various departments In Rikshospitalet 38 per cent were using hearing aids in Ulle vål 28 per cent in Bergen 41 per cent in Namsos 39 per cent in Bodo 31 per cent and in Tromso 19 per cent The second column shows that in all 166 or 8 per cent of the pa tients had been noise expositioned and the third column indicates that 84 or 4 per cent had been exposed to blows/explosions or head traumas Of particular interest is the *question of otosclerosis and pregnancy* The common concept is that the symptoms are ei ther noticed for the first time during pregnan cy or they are aggravated 107 of the 1341 women in the material representing 8 per cent gave such information 92 or 4 5 per cent of the patients also had ear trouble of another origin such as chronic otitis or secre *tory otitis*

SPECIAL CIRCUMSTANCES

	HEARING AIDS	NOISE EXPOSITION	BLOWS	STARTED OR BECAME WORSE DURING PREGNANCY		OTHER DISEASES	TOTAL
					[illegible]		
RIKSHOSPITALET	[illegible]	[illegible]					
ULLEVÅL	[illegible]		1	2			
BERGEN	[illegible]	63	3	1	[illegible]	1	
NAMSOS	42			1	125	3	[illegible]
BODO	53	1		2	[illegible]	1	177
TROMSO	6		1	3	[illegible]	1	31
TOTAL	759	166	84	107	1341	92	[illegible]

Fig 16

obvious that a citizen living in noisy surroundings and compelled to discriminate quickly between different noises has a greater need for good hearing than has a farmer or a lumberjack. The urban population also has a far greater need for speech communication

Thus the varying impulse to contact a doctor is partly dependent upon the environment. There are certainly many cases in the areas mentioned which would show up if we had a better service better information or more E N T clinics It must be concluded that a large part of Norway lies on a poor social level in these respects and in some of our counties the distance to surgical E N T service is far too long

As the majority of otosclerous patients belong to the urban population one might also take into consideration whether differences exist in the age or sex distribution between rural and urban districts However our Statistical Central Bureau has provided the information that during the years in question this factor played no role

Age distribution

The present statistics show that 57 7 per cent of the patients suffering from otosclerosis in Norway are more than 50 years of age while only 1.5 per cent are below 20 years This is not quite in agreement with the findings of Larsson (1960) who found the majority of cases being between 11 and 45 years of age or Morrison (1967) who stated that 91 per cent of his cases were between 15 and 45 years Only 4 per cent in his material were above 45 years of age This weighting towards higher age in Norway must be due to several reasons In the first place the accumulation of cases during the preceding decades must be important. As 23 per cent of the patients were above 60 years of age this implies that Norwegian otologists were late in applying modern operative methods The method was first developed in the greater clinics abroad then applied in the university clinics of Norway and from there brought to outlying clinics In Norway an E N T surgeon in private practice cannot operate in the county clinic unless his chief position is within the hospital Thus some time had passed before the new methods applied abroad were common in our peripheral clinics

Secondly part of the reason may be that our information to the public has been neglected As always this point is a crux medicorum which the doctor postpones if possible and the patients get their information too late It does not suffice to inform only those patients applying for a consultation some public information must also be given in order to bring the knowledge of the usually excellent results of these operations to all possible patients

Inheritance

As related earlier the question of a familial occurrence of loss of hearing is described by referring to the information in the patients records The cases where the loss of hearing in parents or near relatives started in the years above middle age were not considered only those where it started before 45 years of age and where causes for the hearing defects other than the suspicion of otosclerosis were not obvious Such information of course depends upon both the scrutiny of the examining intern and of the patient s own judgement of his relatives hearing Both circumstances call for certain reservations as to the exactness of the obtained information However the statistics seem very convincing 1 049 patients or 50.8 per cent of the material reported loss of hearing among members of their family (Fig 10) Loss of hearing among parents were dominating this was reported by 515 patients but none of these had noted it in both parents The next obvious point was that several patients reported hearing loss in several relatives (Fig 1?) This figure shows in the first place that the inheritance of otosclerosis as also reported by Davis and Silverman (1970) must be due to a gene which may be present in

been much discussed in the literature Shambaugh Jr (1949) also indicated the ratio 3 2 whilst Larsson (1960) and Ballantyne (1960) found it to be 2 1 Altmann (1967) indicated 7 6 Sakai (1971) 1 1 Morrison (1971) also finds the proportion to be 1 1 when including the out patients including only those who received a thorough examination when admitted to a hospital He explains discrepancies by the fact that women often notice their otosclerosis during pregnancy and then demand an examination whereas men are used to working in a more noisy environment where people are talking loud which implies that they do not so easily discover their otosclerosis Thus the later papers show that the proportion of women to men approaches 1 1 when a more thorough examination is performed It is reasonable to believe that this argumentation also might be valid for Norway According to the present statistics there are only one third more women than men not twice as many as most textbooks maintain

Case distribution

As might be expected the majority of cases are found during the years 1964–1967 During these years surgical techniques and microscopes were improved fenestration was replaced by stapediolysis whereupon the scientific literature on the subject grew enormously hence also the popular articles Following this information more patients became aware of the possibility of surgical treatment and hence the number of known cases greatly increased during that period

Geographical distribution

The accumulation of patients in the densely populated areas shown in the two maps of Southern and Northern Norway (Figs 6 7 and Fig 4) must have an explanation There is no proof for the assumption that otosclerosis should be more frequent in denser population and moreover this investigation shows a great difference in the number of patients even between the densely populated areas e g Oslo where there are 7 6 patients per 10000 inhabitants compared to Bergen where there are 13 24 per 10000

Several factors serve to elucidate this discrepancy In Bergen otosclerosis operations were not performed before 1961 At that time periodicals and scientific communications (e g Gundersen 1973) had informed the population about the disease and the operative possibilities As the other clinics performing these operations mainly Rikshospitalet already had long waiting lists the patients had small chances of receiving treatment elsewhere and an accumulation of patients wanting examination and operation occurred So when the opportunity came there was an onrush of patients seeking admissions In addition one must also take into consideration the priorities set by a certain clinic the number of beds in the clinic and the ability and interests of the physicians as factors deciding which cases may be admitted If for instance a clinic like Rikshospitalet has a great press from cases needing cancer surgery otosclerosis patients may receive low priority

The considerations mentioned above explain some of the differences between the densely populated areas differences which are apt to be equalized as the years go by However it is not explained why the incidence is so low in the northern areas Troms (0 32 per cent) and Finnmark (0 2? per cent) and in the mountainous areas in the middle of Norway Hedmark (0 36 per cent) Oppland (0 28 per cent) Aust Agder and Telemark (both 0 26 per cent) If the frequency of cases in Bergen (1 3? per cent) reflects the true incidence there should be from 4 to 6 times as many cases also in these areas

Several factors may serve to explain this uneven distribution In the first place consultations become rarer the longer the distance to the doctor Moreover otosclerosis is a disease one may cope with if the need for communication is moderate as in rural districts It is

obvious that a citizen living in noisy surroundings and compelled to discriminate quickly between different noises has a greater need for good hearing than has a farmer or a lumberjack The urban population also has a far greater need for speech communication

Thus the varying impulse to contact a doctor is partly dependent upon the environment There are certainly many cases in the areas mentioned which would show up if we had a better service better information or more E.N T clinics It must be concluded that a large part of Norway lies on a poor social level in these respects and in some of our counties the distance to surgical E N T service is far too long.

As the majority of otosclerosis patients belong to the urban population one might also take into consideration whether differences exist in the age or sex distribution between rural and urban districts However our Statistical Central Bureau has provided the information that during the years in question this factor played no role

Age distribution

The present statistics show that 57 7 per cent of the patients suffering from otosclerosis in Norway are more than 50 years of age while only 1 5 per cent are below 20 years Thus is not quite in agreement with the findings of Larsson (1960) who found the majority of cases being between 11 and 45 years of age or Morrison (1967) who stated that 91 per cent of his cases were between 15 and 45 years Only 4 per cent in his material were above 45 years of age Thus weighting towards higher age in Norway must be due to several reasons In the first place the accumulation of cases during the preceding decades must be important As 23 per cent of the patients were above 60 years of age this implies that Norwegian otologists were late in applying modern operative methods The method was first developed in the greater clinics abroad then applied in the university clinics of Norway and from there brought to outlying clinics In Norway an E N T surgeon in private practice cannot operate in the county clinic unless his chief position is within the hospital Thus some time had passed before the new methods applied abroad were common in our peripheral clinics

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one generation skip the next and then recur It is not always directly inherited and it may be present in several branches of a family A total of 190 patients reported hearing loss only in the grandparents or more remote relatives In addition this investigation shows that the inheritance is more obvious in Norway than in countries where otosclerosis is not so common Sakai (1971) found positive familial anamnestic information of a progressive hearing loss in only 20 per cent of his cases However to obtain decisive data for a pure genetic investigation the hearing level of relatives would have to be measured On the other hand a hearing loss reported among relatives in more than 50 per cent of the cases is a significant finding Also other data derived from the questionnaire showing 12 5 per cent of the cases reporting hearing loss among their parents and 1 4 per cent among their grandparents is a statistically significant overrepresentation in the families of otosclerosis patients compared to the normal population The result holds true despite faltering statements from the patients and the possibility that some of the reported hearing defects may be due to other diseases like presbyacusis or noise injuries

The number of hearing defects reported among siblings varies according to their total numbers which is not known If the number of siblings vary from one to four the percentage of reported hearing defects vary from 13 7 to 1 9 per cent which are also quite convincing numbers compared to the prevalence of otosclerosis in the whole population −0 3 per cent Since only family members who suffered from hearing defects before the age of 45 were considered the conclusion must be that hearing defects among the parents grandparents or siblings of otosclerotics are far more common than otosclerosis in the whole population

Operations

Of the 2066 cases 1981 were operated on only 85 were not Of these 85 54 were from Rikshospitalet while in Bergen all patients had surgery This is probably primarily due to the fact that in Bergen the patients have to a higher extent been thoroughly examined as out patients and are ready for operation before they are hospitalized whereas Rikshospitalet receives patients from all over the country and the eventual indications for operation must be evaluated after hospitalization Moreover it may also be explained by the surgeons attitude as appears from most data Some are optimistic regarding the advantages of an operation others are more reluctant

It is not the purpose of this study to indicate what surgical methods were actually applied but it appeared from the study of the records that fenestrations are definitively abandoned and so are stapediolyses while stapedectomy is the dominating procedure including all the various prostheses decribed in the literature It is seen in Fig 15 that most patients have had surgery once on one side (1 785) Of course most patients manage if hearing well in one ear but the fact that only 350 had bilateral operations suggests that our otologists possibly because of the risk involved in surgery are reluctant to perform it bilaterally It also appears in Fig 15 that 111 patients have been operated on more than once on the same side a procedure including less risk than bilateral operations

SPECIAL CIRCUMSTANCES

Under special circumstances criteria relevant to otosclerotic disease were recorded

Hearing aids

In this group both those using hearing aids before and after surgery are included They are not divided into separate groups because this would have implied discussing the results of the operations which was not the intention Consequently the data are mostly of social interest. The fact that 3? per cent of the patients had adopted themselves to the use of hearing aids proves that the possibility of acquiring these in Norway is now rather good This is no doubt due to our social security benefits Furthermore the numbers of hearing aid users both before and after surgery can be taken as evidence for the value of these devices Hence the otologist must consider for each patient not only the relevance of surgery but the possible benefit of applying a hearing aid

Noise

Here those patients are included who stated to have been exposed to noise to such an extent that it might have influenced their hearing These were 166 or 8 4 per cent which seems to be a small figure indicating that noise represents no major problem in this connection These patients do not percei e the noise as easily as those with normal hearing However according to the present knowledge of the damage in the auditory system caused by noise it is obvious that a postoperative noise exposition will be particularly disabling to such patients Therefore as a general rule they are advised to a oid working in a noisy environment

Blows, explosions and head traumas

84 patients or 4 per cent, had been exposed to these traumas a considerably lower figure than expected There is no reason to expect traumas to have any etiological significance concerning otosclerosis but the greater part of this material consists of patients more than 50 years of age who have lived through the war in Norway which must have afflicted a sensorineural hearing loss on some However the number of patients affected by such conditions is not so large as to require a more exhaustive discussion nor does it interfere with the other statistical data.

Pregnancy as a precipitating factor

Morrison (1971) stated that 12 per cent discovered the disease during pregnancy and another 4? per cent had an aggravation of the hearing loss during pregnancy In Handbuch der Ohrenheilkunde (Marx 1938) the hearing loss in otosclerosis is said to increase with the number of pregnancies This occurs to 30 per cent at the first to 60 per cent at the second and to 80 per cent if there are three pregnancies or more This is in Scandinavia as well regarded as an axiom and is stated in all text books Still there is a long step from the 8.3 per cent Norwegians who stated that they discovered initial or worsening hearing loss during pregnancy to the 4 per cent referred by Morrison or the 30 per cent referred by Marx Even if one takes into consideration the imperfect records where the difference between the pregnancies was not always pointed out the 8.3 per cent cannot be particularly wrong. The conception that the hearing loss in otosclerosis increases during pregnancy is so well implanted into the minds of E N T interns that the point was seldom omitted during the elaboration of the records Possibly the increasing considerations for the womens condition during pregnancy and the improved living conditions play a role so that several features during pregnancy are improved including the hearing deficiency Scientists are now discussing whether the symptoms actually do tend to start or increase as a result of preg

nancy One should remember that the age where the greatest incidence of this disease occurs coincides with the age of pregnancies and the earliest osseous changes start long before the symptoms are discovered In the present study 1341 of the 2066 patients were women 107 or only 8 3 per cent stated that they noticed the disease or it became worse during pregnancy This low figure suggests that the deep-rooted idea of worsening during pregnancy may have to be revised

Other diseases

92 patients or 4.5 per cent had additional ear diseases There is no statistics showing the number of acute chronical or secretory otitis but the figure 4.5 per cent agrees with the number of hard of hearing persons in a normal population (Hall 1956 Ballantyne 1960 Davis & Silverman 1970) It seems reasonable *to assume that the predisposition for otosclerosis* is not related to any general tendency toward ear diseases

Summary and Conclusions

The records of all patients suffering from *otosclerosis from the six clinics of Norway* which offered surgical treatment of this disease were studied for the period 1960–1969

During the decade 1960–1969 there were in Norway 2066 patients admitted to these clinics which means that at any time there is approximately 0 3 per cent of the population suffering from this disease

The proportion of women to men was 3 2 *which does not confirm the previous assumptions* that otosclerosis is twice as frequent in women as in men

There was a higher frequency of patients in the densely populated areas which is quite reasonable in view of the better opportunity to treatment There were about twice as many cases per inhabitant in Western Norway i e in the city and surrounding districts of Bergen as in Oslo which is probably due to the fact that in the former district one did not start otosclerosis surgery until 1961 and this led to an accumulation of patients waiting for admittance

These conditions are also reflected in the age distribution In previous studies only 4 per cent were over age 45 whereas in Norway 58 *per cent were above age* 50

51 per cent of the patients stated that some of their closer relatives suffered from a loss of hearing at an early age The present material confirms the findings of previous authors that hearing losses occur much more frequently in the patients parents grandparents and siblings *than among the rest of the population*

96 per cent of the patients were operated upon 70 *per cent* unilaterally 22 per cent bilaterally The method of choice was the stapedectomy with varying types of prostheses

37 per cent of the patients were using or had been using hearing aids

Only 8 per cent of the patients complained that noise aggravated their disease

Only 8 per cent of the women stated that the symptoms started or worsened during pregnancy This low figure shed doubt on the assumption that pregnancy tend to worsen otosclerosis

Otosclerosis also occurs in the Lapp population in Norway We have evidence that in three members of this race otosclerosis was diagnosed and oper[illegible] performed

Résumé et Conclusions

Les documents sur l otosclérose provenant des six cliniques norvégiennes opérant cette maladie ont été analysés pour la période 1960-1969

A cause de difficultés practiques nous n avons pas obtenu comme attendu, un aperçu pour la population lapone mais il s est montré que jusqu à maintenant trois Lapons ont été opérés pour cette maladie L otosclérose existe donc aussi chez les Lapons

Dans la période 1960-1969 il a été enregistré en Norvège 2066 patients souffrant d'otosclérose Ce qui signifie qu en moyenne 0,3 pour cent de la population souffre de cette maladie.

La proportion femme homme était de 3 2 ce qui ne confirme pas tout à fait les précédentes suppositions que l otosclérose est deux fois plus répandue chez les femmes que chez les hommes

Il y avait une majorité de patients provenant de régions fortement peuplés ce qui est naturel quand on considère que l accès aux traitements est plus aisé Il y avait environ deux fois plus de cas par habitant sur la côte ouest aux environs de Bergen qu à Oslo ce qui probablement est dû au fait qu on a commencé à opérer l otosclérose à Bergen qu à partir de 1961 Il y avait alors un grand nombre de patients qui avait attendre un traitement

On retrouve la même situation en ce qui concerne la répartition d après l âge Précédentes études ont montré que seulement 4 pour cent avait plus de 45 ans tandis qu en Norvège 58 pour cent des patients avaient plus de 50 ans

51 pour cent des patients ont indiqués une réduction de l ouïe en relative bas âge chez les parents

Le matériel rassemble confirme ce qui a été trouvé dans de précédentes recherches La réduction d ouïe chez les parents des patients souffrant d otosclérose est beaucoup plus fréquente que l otosclérose chez le reste de la population

96 pour cent de patients ont été opérés 70 pour cent de ceux-ci ont été opérés une fois d un côté 22 pour cent ont été opérés des deux côtés La méthode d opération était la stapedectomie avec de différents types de protèse

37 pour cent des patients utilisaient ou avaient utilisé un appareil auditif

Seulement 8 pour cent des patients se plaignaient que le bruit semblait avoir aggravé leur cas

Seulement 8 pour cent de femmes ont indiqués que les symptômes avaient commencé ou s étaient aggravés durant la grossesse ce qui est une si petite proportion qu on peut douter de la supposition que la grossesse aggrave l otosclérose

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Sincere thanks are also due to the heads of the other otolaryngological clinics who all so willingly let me examine their records Professor T Leegaard Professor E Steen Dr H Fabritius Dr A Gulsvik and to the head of the Institute of Social Medicine University of Oslo Professor P Sundby for valuable advice in interpreting the results

The author also wishes to thank Miss S Hall and Mr A Ferber for the statistical ana-

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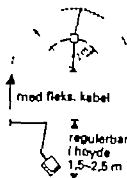
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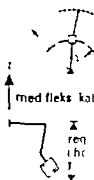
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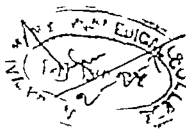
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BY

SEPPO KARJALAINEN

From the Department of Otolaryngology
University of Oulu, Finland

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Kirjapaino Osakeyhtiö Kaleva
Oulu Finland 1974

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INTRODUCTION

Many tests have been developed during the last decades for the differential diagnosis of sensori-neural hearing loss. Recruitment measurements have particularly attracted the audiologist s interest because loudness recruitment has been found to be associated with the lesions in the organ of Corti Dix, Hallpike & Hood (1948) demonstrated positive recruitment particularly in Ménière s disease and showed further that it does not occur in connection with lesions of the VIII cerebral nerve or higher acoustic centres. Similar results have been reported by Eby & Williams (1951) Lundborg (1952) Kristensen & Jepsen (1952) and Dix & Hallpike (1958) However some authors have also found mostly partial but sometimes even complete loudness recruitment also in conductive hearing loss (Palva & Ojala 1955 Anderson & Barr 1968 Kärjä 1970) This phenomenon is considered mechanical in nature and not due to *receptor organ lesions*

Tests for loudness recruitment can be divided into the direct and the indirect. The latter attempt to measure the rate of loudness increase they include particularly the intensity difference limen tests (Lüscher & Zwislocki 1948, 1949 Denes & Naunton 1950 Hirsh et al. 1952) and in borderline cases, automatic threshold audiometry (Reger & Kos 1952, T Palva 1957) For testing minor excursions in cases of recruiting deafness, the last mentioned is the only indirect test to remain in widespread use

Direct tests of loudness recruitment can be performed on a great majority of patients and obviously are the procedure of choice in its detection and measurement. In these supra threshold tests, the increase in loudness at a certain frequency in the affected ear is directly compared with that in the normal ear at the same frequency (Fowler 1928 1936) or at two different frequencies (Reger 1936) one tested with normal and the other with impaired hearing.

In Fowler s Alternate Binaural Loudness Ba lance (ABLB) test, it is presupposed that one ear has normal or nerly normal hearing The tone can be switched over from one ear to the other either manually or automatically For physiological reasons, the rise-decay time of the tone must be short enough (50 msec) and identical for both ears. To avoid adaptation and auditory fatigue the sound should be short, 0.3—0.5 sec (Lidén 1962) but not *shorter than* 200 *msec* (Munson 1947 Garner 1947) In some studies the comparison has been carried out by measuring the loudness balance *of the tones* simultaneously in both ears, but Hood (1950) showed that the results were not always reliable even in clear *cases of* recruitment. Indeed in these cases interaural localization is *substituted* for loudness balance proper and the mechanisms are different

The *ABLB* test can be carried out at any frequency and Fowler presented the results of the loudness balance either in a system of coordinates as the function of the reference and test tone, or by a columnar scale graph

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Direct tests of loudness recruitment can be performed on a great majority of patients and obviously are the procedure of choice in its detection and measurement. In these supra threshold tests the increase in loudness at a certain frequency in the affected ear is directly compared with that in the normal ear at the same frequency (Fowler 1928 1936) or at two different frequencies (Reger 1936) one tested with normal and the other with impaired hearing

In Fowler's Alternate Binaural Loudness Ba lance (ABLB) test it is presupposed that one ear has normal or nerly normal hearing The tone can be switched over from one ear to the other either manually or automatically For physio-logical reasons, the rise-decay time of the tone must be short enough (50 msec) and identical for both ears To avoid adaptation and auditory fatigue the sound should be short, 0.3—0.5 sec (Lidén 1962) but not shorter than 200 msec (Munson 1947 Garner 1947) In some studies the comparison has been carried out by measuring the loudness balance of the tones simultaneously in both ears, but Hood (1950) showed that the results were not always reliable even in clear cases of recruitment. Indeed in these cases interaural localization is substituted for loudness balance proper and the mechanisms are different.

The ABLB test can be carried out at any frequency and Fowler presented the results of the loudness balance either in a system of coordinates as the function of the reference and test tone or by a columnar scale graph.

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The ABLB test can be carried out at any frequency and Fowler presented the results of the loudness balance either in a system of coordinates as the function of the reference and test tone, or by a columnar scale graph

Reger's monaural loudness balance test is applicable to cases in which the hearing defect is bilateral but of different degree at different frequencies. Comparison is carried out using two frequencies monaurally at one or several supra-threshold levels. The reference tone usually chosen is 1000 Hz but if it is impaired by the same degree as the test tone, a generally lower reference tone is chosen. Since the frequencies with a normal threshold can be either in the same or contralateral ear as the test tone, the measurement can in principle be either monaural or binaural. Reger suggested 30 dB as the necessary threshold difference between the tested frequencies since loudness comparison is more difficult in the monaural than the binaural test.

Loudness correlation of different frequencies, the phon contours, were published by Kingsbury (1927) and by Fletcher & Munson (1933), and were further amplified by Churcher & King (1937). These experiments employed the manual testing techniques using the method of adjustment or the method of constant stimuli, both with earphones and in the free field. In normally hearing test subjects, with 1000 Hz as the reference tone, a phenomenon similar to loudness recruitment appeared at low and high frequencies. This has an immediate implication on the Reger's test which in effect is based on normal equal loudness level contours.

In recent years, self-recording Békésy-type automatic audiometry has become widespread for various audiologic tests. In addition to its versatile use for both threshold and supra-threshold tests, the recording procedure itself makes it possible to employ the method of adjustment for the patient's responses. Using the method of limits or constant stimuli, there is a certain interaction between the examiner and the test subject, whereas self-recording provides another type of response in which the examiner has no essential part. In this study, one of the purposes has been to test how well the phon contours can be reproduced by the automatic recording technique in normally hearing persons. The task of making recordings of a loudness balance of two tones different both in frequency and intensity might prove very difficult, if not impossible, without guidance from the examiner. Furthermore, the results, if reliable and reproducible, have a direct correlation to Reger's test at various frequencies. Stated in more detail, this study aims, by comparing the automatic testing techniques on a normal material, to

— investigate whether automatic audiometry can be used for reliable loudness level comparison at various frequencies and to
— compare these results with the classical phon contour data.

Further, the data will be used to

— find out how the size of the threshold excursions varies at various test combinations, to
— find out whether the results obtained by monaural or binaural testing techniques are different, to
— study how well frequencies that are far apart can be used for loudness matches and to
— transform the normal values of loudness comparison between various pure tones into a scale graph in order to obtain normal references for the Reger test with automatic audiometry.

EARLIER STUDIES ON EQUAL-LOUDNESS CONTOURS

The first extensive study of the intercorrelations of the loudness levels of pure tones was published by Kingsbury in 1927. He examined 22 subjects to whom the stimulus was given monaurally through a high-impedance ear phone. The reference tone was 700 Hz with which 11 other frequencies, ranging from 60 to 4000 Hz, were compared. The highest intensity levels used were up to 90 T U (transmission units equal to dB) above the 700 Hz threshold. Comparisons were made at 10 dB intervals. The equipment consisted of two oscillators, one giving the reference tone and the other the test tone the intensity of which was manually adjusted by the subject himself. The attenuator dial of the latter oscillator was covered by cardboard to prevent the test subject from seeing it. Duration of the sound impulses used was not indicated.

Kingsbury concluded that if the amplitude of the various test frequencies was raised at equal steps the low tones increased in loudness much more rapidly than the high ones. For frequencies above 700 Hz the rate of loudness level increase was found to be nearly uniform.

Basic work on equal-loudness levels at threshold was made by Sivian & White (1933). These measurements were carried out using tones ranging from 100 to 15000 Hz for monaural hearing and from 60 to 15000 Hz for binaural hearing on 13 observers. At 1000 Hz the minimum audible field corresponded to a pressure of 71 dB below 1 bar. Another set of measurements were made concerning minimum audible pressures measured at the observer's ear drum. The slightly different threshold values obtained were explained as being due to wave motion in the ear canal and and to diffraction caused by the head.

Fletcher and Munson published their classic study in 1933 using the sound stage and the technique of measuring field pressures as described by Sivian & White (1933). The voltage levels in the earphones were thus compared to those of loudspeakers giving equally loud tone sensations in a free field. Their series comprised 11 test subjects using binaural earphones. Threshold measurements were made before and after the loudness level comparison using the same circuit. The constant stimulus method, under which the test subject simply stated which of the two tones was louder or softer, was used for the comparison. The test tones consisted of ten frequencies within the range of 62-16000 Hz, and the reference tone was 1000 Hz, the test subjects sitting in a sound proof booth. They first heard the test tone and 0.5 sec later the reference tone, the two sounds lasting 1 sec each. This was followed by a pause of 1 sec and the same sequence was repeated. The rise-decay time of the sound impulses was about 0.1 sec. Comparison levels extended from threshold values up to c. 115 dB. Fletcher and Munson discovered that their equal loudness contours were similar to those of Kingsbury between 100 and 2000 Hz, while differences in both directions were observed at lower and higher frequencies. The authors

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Churcher & King (1937) carried out an extensive equal loudness determination with pure tones by means of free-field stimulation The study comprised 30 test subjects in groups of 10 who made the comparison with the constant stimulus method. The testing technique was manual in the same way as in the work by Fletcher & Munson (1933) The reference tone was 1000 Hz, and the test tones ranged from 54-9000 Hz. The duration of the sound impulses to be compared for the level of loudness was 2 sec and they were heard in rapid succession After a pause of 10 sec the sequence was repeated. The equal loudness level comparisons were made up to the level of 90 dB and the reference tone was increased by 10 dB steps

With free field stimulation a higher intensity than in the studies summarized above was required for the low frequency in order to equal the 1000 Hz loudness level at low stimulation levels. At the 80—90 phon level the divergence from Fletcher and Munson s curves was in the opposite direction The authors concluded that at frequencies higher than 1000 Hz the differences between receiver and free-field measurements are due to experimental errors while below 1000 Hz the differences are due to the two methods themselves

Zwicker & Feldkeller (1955) were the first to use automatic test technique in their study They had eight test subjects who listened to 0 6 sec long stimuli monaurally through an ear phone Loudness balances were made conti nuously according to the Békésy tracking technique The reference tone was 1000 Hz, and the test tones ranged from 50 to 20 000 Hz. Comparison was carried out in 10 dB steps up to the level of 90 dB at 1000 Hz. At first the test subject heard e.g a 500 Hz tone which changed continually by 1 dB/sec After 0 6 sec the 400 Hz tone disappeared and the subject heard the reference tone which remained constant in intensity After another 0 6 sec this was replaced by the test tone The test subject adjusted the test tone by switch control making it louder or softer In the course of the experiment the test tone changed continually so that the whole scale of frequencies was covered within 15 minutes. The measurements revealed that it was best to start the comparison from 1500 Hz and work downwards and again from 700 Hz upwards.

The equal loudness level contours of Zwicker & Feldtkeller (1955) were clearly more widely separated from each other at the low frequency — low stimulation levels than those of Fletcher & Munson (1933) Compared with the results by Churcher & King (1937) uniformity was poor at the high frequencies the self recorded values distinctly exceeding the free-field curves

Robinson & Dadson (1956) made an extensive study with pure tones using free field stimulation The constant stimulus method was used and the series consisted of nine test subjects. Frequencies ranging from 25 to 15000 Hz were used in the comparison and the sound pressure levels extended to 130 dB re 0 0002 dyn/cm² The most common reference tone was 1000 Hz, but comparisons were carried out with other pairs of frequencies also primarily to ensure the constancy of the equal loudness relations The duration of sound impulses varied between 1—3 sec depending on the frequencies compared Because of threshold deviation and the resulting disturbance in loudness compa rison no comparisons were made at levels below 20 dB The studied frequencies were given alternatingly in the sequences AOBOAOB and BOAOBOAOB where A was the reference stimulus and B the test sound while O was the pause. The switching was complete at 0 15 sec The B sound varied over a wide scale of the sound pressure level so as to include with an adequate margin the transition levels of all observers A new feature noted in the results compared with those reported earlier was a dip in the contours between 400 and 500 Hz which was at its maximum on the middle levels

Recently Ross (1967) made a loudness level comparison study with three test subjects The stimuli were applied by an earphone through individually moulded ear inserts and sound pressures were measured at a distance of a few mm from the eardrum Thirteen frequencies

from 20 to 5000 Hz were compared. By pairs, each was once the reference tone and once the test tone. For threshold determination the duration of the sound impulse was 1.25 sec, and the same in the loudness comparisons. The reference and test tones were given consecutively without a pause. The test subject himself manually adjusted the intensity of the test tone. The comparison was carried out at 5 dB intervals beginning from values just above the threshold, and continued as high as the test subject could tolerate.

The equal-loudness-level contours obtained were similar to those reported from earlier studies but their rise was steeper at the low frequencies

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Both channels were led to the earphones via a switch box with which the examiner could direct either sound to the right or the left earphone. The head receivers were Beltone TDH 39 earphones mounted in MX41/AR cushions. The frequency response characteristics of the ear phones are shown in Fig. 2.

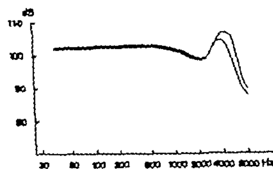


Fig. 2. The characteristics of earphones

The intensity of the test tone in channel 1 was controlled by the test subject with a press button switch he held in his hand. The rate of intensity was 2.1 dB/sec. All measurements were made using the SPL intensity scale of the Grason Stadler audiometer. The sound pressure levels in the earphones at 60 dB setting (Table 1) and with a fixed input of 0.1 V were calibrated using a 6 cc artificial ear and the Brüel—Kjaer measuring equipment. The 10 dB intensity steps of the audiometer intensity scale for both test and reference tone were checked for the whole frequency range tested up to the level of 115—120 dB and were found to be accurate.

Table 1. *The sound pressure levels in the earphones at 60 dB setting re 0.0002 dyn/cm*

Frequency	Right earphone	Left earphone
125	61	61
250	65	66
500	66	66.5
1000	64.5	67.5
2000	66	69
3000	65	68.5
4000	69	68
6000	68	64
8000	70	71.5

B Material and testing technique

The series examined consisted of 14 healthy test subjects who with one exception had never before attended an audiologic examination. Their ages ranged from 14 to 29 mean 24 years. The subjects selected had no known history of ear diseases and their eardrums were examined and found intact before hearing thresholds were measured. Every subject admitted to the final equal loudness measurement had, on the basis of the threshold measurements, normal hearing in both ears at the frequencies of 125 250 500 1000 2000 3000 4000 6000 and 8000 Hz.

Hearing thresholds were measured only once since otherwise the test period would have become too long and the subjects might not have been able to concentrate on the tests of loudness level comparison.

By connecting the Philips generator to the electronic switch alternate stimulus input jack for the time of the measurements, the thresholds of the frequencies serving as reference could be registered with the automatic Békésy audiometer. The midpoint of the excursions was considered the threshold value.

Since it is known that the hearing threshold normally varies slightly depending on the subject s degree of fatigue and mental state, the threshold values for the equal loudness level measurements were selected by rounding off the mean values of the excursions to the nearest 5 dB.

Hearing thresholds were measured using continuous test tones which by-passed the interrupter. This was done because the interrupter produced a weak background noise in the earphones. The noise however was so soft that it could not be measured owing to the environmental noise of less than 25 dB in the examination room. The noise produced by the interruptions did not increase when comparison advanced to the higher soundpressure levels.

Before starting the threshold measurements the subjects were instructed to press the button in their hand when they heard the sound and to release the button when the sound disappeared.

EQUIPMENT MATERIAL AND TESTING TECHNIQUE

A Equipment

The study was carried out in the Audiological Laboratory of the Otolaryngological Department of Oulu University The equipment and the test subject were situated in separate sound proof rooms with a partition wall fitted with a triple-pane window The background noise measured (Precision Sound Level Meter Type 2203 Brüel and Kjaer Denmark) in the test room was less than 45 dB SPL re 0 0002 dyn/cm² Analysed by means of an octave filter (Type 1613 Brüel and Kjaer) the noise was found to consist of frequencies below 250 Hz In octave bands at the mean frequencies of 125 250 500 1000 2000 3000 4000 6000 and 8000 Hz, the attenuation rate being about 45—50 dB/octave the noise never exceeded 25 dB re 0 0002 dyn/cm²

The test arrangement is shown in Fig 1 The source of the test tones was a Grason Stadler Model E 800 Békésy audiometer the tones being led to channel 1 The reference tone was obtained from a Philips GM 238 sound generator and it was connected to the external input jack of the Grason Stadler audiometer and further to channel 2 The continuous tones from both sound sources were led to an interrupter which transformed them into 400 msec long pulses coming on alternatingly with a pause of 400 msec between them The rise and decay times were 30 msec each

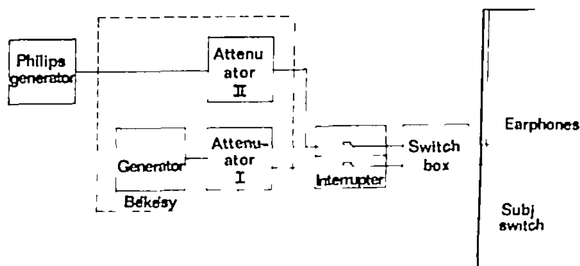


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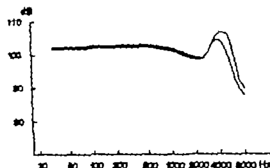


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Every frequency measured was registered for one minute The first equal loudness measurement was carried out 15 minutes after the threshold measurements or if threshold determination had taken an unusually long time or the test subject felt tired not until the following day

The frequency pairs compared were 4000—8000 4000—6000 3000—8000 3000—6000 3000—4000 2000—8000 2000—6000 2000—4000 2000—3000 1000—8000 1000—6000 1000—4000 1000—3000 1000—2000 1000—500 1000—250 1000—125 500—4000 500—2000 500—1000 250—4000 250—2000 250—1000 250—500 125—2000 125—1000 125—500 125—250 Hz. The first frequency of the pairs was the reference tone and the second the test tone

Comparison was carried out both mon and binaurally One half of the test subjects began with the monaural and the other with the binaural test In the monaural test both tones entered the right ear while in the binaural test the reference tone was always fed to the left ear and the test tone to the right ear Before the examination began the test subject was given a detailed description of his task during the test At first he heard only the reference tone but soon afterwards also the test tone The subject was requested to concentrate only on the loudness level of the frequencies compared and pay no regard to their different pitch When the test tone began to sound louder than the reference tone he pressed the control button and if the opposite was the case he could obtain a louder test tone by releasing it When the comparison began the author did not try to give the test tone "at the right level but let the test subject find the equal loudness level.

One minute per compared pair was allowed for the balancing The study was started at the 20 dB sensation level and continued on later days at 40 60 and 80 dB levels On the last day the comparison was carried out at almost the maximum intensity of the audiometer the reference tone reaching 60 dB at 125 Hz, 80 dB at 250 Hz 100 dB at 500 and 1000 Hz and 90 dB SL over 1000 Hz. If possible the comparisons were carried out at the various levels on consecutive days in order to avoid the test subjects catching diseases such as colds, coughs etc that might possibly affect their hearing during the examination On transition from a monaural to a binaural test a pause of 15 min was allowed In some cases e g owing to tiredness the latter half of the comparison had to be carried out the next day

TREATMENT OF DATA

Computer treatment of data was carried out using the BMD library programme O5R of UNIVAC 1108 (BMD = Biomedical Computer Programmes). The values of every pair of pure tones tested on the subject (e.g. 1000 Hz — 3000 Hz) were punched on cards, one pair per card (e.g. 030006). The equation selected for the curve to be calculated was the third-power polynomial $Y = A + BX + CX^2 + DX^3$ which in the trial run was found to illustrate best the equation of all the pairs of pure tones.

In the computer run the so-called parameter cards were added to the above value cards. The parameter cards indicate the number of the values (value cards) of the relevant test frequency pair the power of the equation to be calculated (3) and a few other points associated with computer treatment. The card material obtained in this way was sent from the Oulu University Computer centre to UNIVAC in Helsinki.

The library programme O5R calculates from the material the mean values, standard deviations, the value of the constant (A) regression coefficients (B C and D) the table for variance analysis, and the F value. The programme also gives the X and Y values and the polynomial values equalling the X values (the calculated values of Y) as well as the difference between the true and calculated values of Y. The X values are always reference frequency values and the Y values represent the test frequency.

Mathematical treatment

Programme O5R reads the X values (independent variable) and the Y values (dependent variable).

It is written

$$Z_{ij} = X_i^j \quad \text{where } i = 1 \ldots n \text{ (number of values)}$$

$$j = 1 \ldots k \text{ (polynomial degree)}$$

Product sums are calculated after the mean values have been subtracted from Z_{ij} and Y_i

$$W = \sum_{k=1}^{n} (Z_{ki} - \bar{Z}_i)(Z_{kj} - \bar{Z}_j)$$

$$t = \sum_{k=1}^{n} (Z_{ki} - \bar{Z}_i)(Y_k - \bar{Y})$$

$$S = \sum_{k=1}^{n} (Y_k - \bar{Y})$$

Regression coefficients are obtained by transposing the matrix W and multiplying it with t.

Value F shows how well the polynomial can be calculated from the material given. The table yields:

$F(1\ 60) = 7.08$ $(P = 0.01)$ which means that the material is statistically reliable.

Every frequency measured was registered for one minute The first equal loudness measurement was carried out 15 minutes after the threshold measurements or if threshold determination had taken an unusually long time or the test subject felt tired not until the following day

The frequency pairs compared were 4000—8000 4000—6000 3000—8000 3000—6000 3000—4000 2000—8000 2000—6000 2000—4000 2000—3000 1000—8000 1000—6000 1000—4000 1000—3000 1000—2000 1000—500 1000—250 1000—125 500—4000 500—2000 500—1000 250—4000 250—2000 250—1000 250—500 125—2000 125—1000 125—500 125—250 Hz. The first frequency of the pairs was the reference tone and the second the test tone

Comparison was carried out both mon and binaurally One half of the test subjects began with the monaural and the other with the binaural test In the monaural test both tones entered the right ear while in the binaural test the reference tone was always fed to the left ear and the test tone to the right ear Before the examination began the test subject was given a detailed description of his task during the test At first he heard only the reference tone but soon afterwards also the test tone The subject was requested to concentrate only on the loudness level of the frequencies compared and pay no regard to their different pitch When the test tone began to sound louder than the reference tone he pressed the control button and if the opposite was the case he could obtain a louder test tone by releasing it When the comparison began the author did not try to give the test tone at the right level but let the test subject find the equal loudness level

One minute per compared pair was allowed for the balancing The study was started at the 20 dB sensation level and continued on later days at 40 60 and 80 dB levels On the last day the comparison was carried out at almost the maximum intensity of the audiometer the reference tone reaching 60 dB at 125 Hz, 80 dB at 250 Hz 100 dB at 500 and 1000 Hz and 90 dB SL over 1000 Hz If possible the comparisons were carried out at the various levels on consecutive days in order to avoid the test subjects catching diseases such as colds, coughs etc that might possibly affect their hearing during the examination On transition from a monaural to a binaural test a pause of 15 min was allowed In some cases e g owing to tiredness the latter half of the comparison had to be carried out the next day

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RESULTS

A General aspects

The test subjects carried out the equal loudness comparison at 20 40 60 and 80 dB sensation levels Ten subjects took part in comparison at the maximum level The sensation levels are approximative considering the described rounding off of the threshold level to the nearest 5 dB

The method of adjustment with the self recording audiometer used to carry out the comparison requires greater concentration by the test subject than the constant stimulus method or the method of limits common in the earlier studies. Some test subjects could not manage to carry out the comparison within one minute their Békésy excursions showing a continuous, either rising or falling trend One test subject had to be excluded because he on re-testing repeatedly chose a loudness level differing by up to 15—20 dB from his earlier result

Probably most of the above exclusions must be attributed to fatigue for the studies had to be carried out in the evening after the day s work Normally however the test subject on re-testing even after an interval of several days again chose the earlier balancing level with an accuracy of ±5 dB Having achieved a balance most test subjects maintained it with an accuracy of 0—5 dB

B Threshold measurements

Threshold measurements usually took c 45—60 minutes including the initial familiarisation with the test and the 10-minute interval after testing the first ear A mean value curve was calculated for the material from these measurements based on the arithmetic means (Table 2) The two ears displayed an equal hearing ability at low frequencies up to 1000 Hz but at high frequencies the left ear was slightly better (Fig 3) The difference was over 3 dB at its maximum at 3000 Hz, but t test showed that it was not significant When the standard deviation of the threshold values was calculated the much better than average values of the youngest test subject (14 yrs) attracted attention When he was excluded the standard deviations were clearly reduced This subject is, however included in the study and its statistical treatment since despite his young age he made the comparisons without the slightest difficulty

Table 2. *Mean values of thresholds relative to 0 0002 dyn/cm*

Frequency	Right ear		Left ear	
	mean	SD	mean	SD
125	47 6	9 9	49 4	11 1
250	26 9	8 7	25 9	10 5
500	11 9	7.3	13 1	8 2
1000	11 4	4 7	10 0	6 0
2000	11 1	5.5	9.5	7 0
3000	12.8	5 9	9 4	6.3
4000	14 4	6 1	12.3	5 7
6000	14 4	7.5	17.3	8.5
8000	13.2	9 6	13 2	8 8

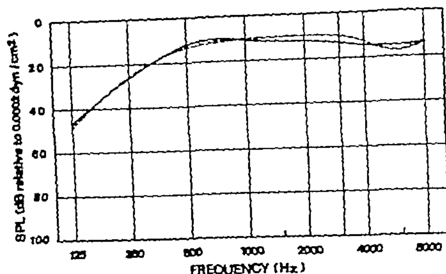


Fig 3. The continuous line is the threshold curve of the right ear and the broken line that of the left ear

C Amplitudes of balancing excursions

1 *Threshold level.* In threshold determinations the amplitudes of Békésy excursions ranged from 5 to 19 dB and in the balancing periods from 3 to 23 dB.

Table 3 shows that the excursions were slightly greater at low frequencies, but no significant differences appeared. Neither were significant differences noted between the left and right ears.

2. *Suprathreshold level.* The amplitudes of balancing excursions (all averaged) tended to diminish at high comparison levels (Table 4). The difference was significant in the monaural study between levels 20 and 60, 20 and 80 and 20 and the maximal sensation level. In the binaural study the difference was significant between sensation levels 20 and 60, and 20 and 80 dB. At the maximal level the amplitude of the excursions again tended to increase. Between the mon- and binaural study no significant differences were noted in the excursion amplitudes at any level ($p \leq 0.05$)

Table 3. *Average amplitudes of threshold excursions (dB)*

Frequency	Right ear		Left ear	
	mean	SD	mean	SD
125	10.7	3.7	10.3	2.6
250	9.9	2.4	9.6	2.4
500	9.9	2.9	9.9	2.0
1000	9.5	2.4	9.2	1.6
2000	9.2	2.6	9.2	2.2
3000	7.9	2.1	8.1	1.9
4000	8.4	2.1	8.6	2.0
6000	8.8	2.1	9.3	2.8
8000	9.1	2.9	9.1	2.6

Table 4. *Average amplitudes of balancing excursions (dB)*

SL	Monaural			Binaural		
	mean	SD	NO	mean	SD	NO
20	11.0	2.4	352	11.0	2.5	352
40	11.1	2.8	383	11.1	2.6	383
60	10.5	2.1	383	10.4	2.3	375
80	10.0	2.1	332	9.8	2.1	328
max	10.3	2.6	230	10.4	3.1	228

NO = number of observations
SL = sensation level
SD = standard deviation

RESULTS

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Threshold measurements usually took c. 45—60 minutes including the initial familiarisation with the test and the 10-minute interval after testing the first ear A mean value curve was calculated for the material from these measurements based on the arithmetic means (Table 2) The two ears displayed an equal hearing ability at low frequencies up to 1000 Hz but at high frequencies the left ear was slightly better (Fig 3) The difference was over 3 dB at its maximum at 3000 Hz, but t test showed that it was not significant When the standard deviation of the threshold values was calculated the much better than average values of the youngest test subject (14 yrs) attracted attention When he was excluded the standard deviations were clearly reduced This subject is however included in the study and its statistical treatment since despite his young age he made the comparisons without the slightest difficulty

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500	11 9	7.3	13 1	8.2
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2000	11 1	5.5	9.5	7.0
3000	12 8	5 9	9 4	6.3
4000	14 4	6.1	12.3	5 7
6000	14 4	7.5	17.3	8.5
8000	13 2	9 6	13 2	8 8

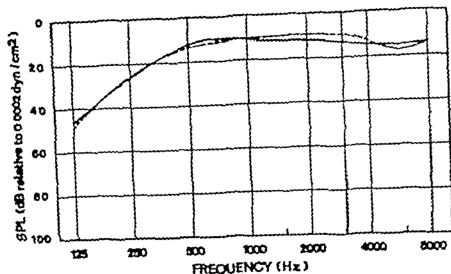


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125	10 7	3 7	10.3	2.6
250	9 9	2.4	9 6	2.4
500	9 9	2.9	9 9	2.0
1000	9.5	2.4	9.2	1.6
2000	9 2	2.6	9.2	2.2
3000	7 9	2.1	8.1	1 9
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The method of adjustment with the self-recording audiometer used to carry out the comparison requires greater concentration by the test subject than the constant stimulus method or the method of limits common in the earlier studies. Some test subjects could not manage to carry out the comparison within one minute, their Békésy excursions showing a continuous, either rising or falling trend. One test subject had to be excluded because he, on re-testing, repeatedly chose a loudness level differing by up to 15—20 dB from his earlier result.

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Frequency	Right ear		Left ear	
	mean	SD	mean	SD
125	47.6	9.9	49.4	11.1
250	26.9	8.7	25.9	10.5
500	11.9	7.3	13.1	5.2
1000	11.4	4.7	10.0	6.0
2000	11.1	5.5	9.5	0
3000	12.5	5.9	9.4	6.3
4000	14.4	6.1	12.3	5.
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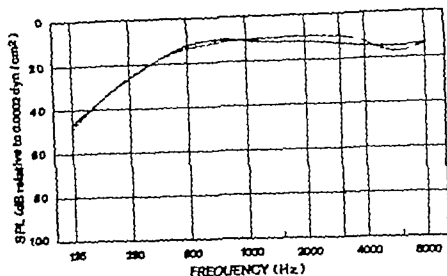


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D Matching functions between pure tones

When matching functions between pure tones were drawn from the values calculated by computer the initial point (threshold values) of the functions was taken as the arithmetic mean threshold value defined above This was necessary because in this way the first curve of the equal loudness-level contours drawn with the aid of matching functions became indentical with the threshold curves. The computer calculated the mean values of both frequencies for the system of coordinates with the least squares method in both directions from the centre of the curve. For this reason the points at both ends of the function are partially determined also by the location of the points along the curve. When the computer-calculated threshold values were compared with the arithmetic threshold values, the difference was found to be at the most 2—3 dB and in many cases the values were the same.

The figures 4—7 show the graphs of the matching functions between pure tones.

As was stated (p. 11) the sensation levels are approximative. For this reason the standard deviation values were not calculated separately for each sensation level of the matching functions, but the computer programme was so selected that standard deviation values were obtained directly for the whole curve (Table 7) The SD values at low frequencies are distinctly higher when they serve as the reference tone

E. Equal-loudness level contours

1 *Phon contours*

The loudness level of a given tone in terms of phons is equal to the sound pressure level (re 0.0002 dyn/cm²) of a 1000 Hz tone that to subjects with normal hearing sounds equally loud as the tone concerned. Phon contours were drawn with the aid of frequency pairs in which *1000 Hz was the reference tone The threshold* contour is at the same time the 0 phon contour A comparison of the mon- and binaural phon contours reveals that the former needed slightly less intensity for equal loudness than the binaural test at both low and high frequencies (Fig 8)

2. *Other equal-loudness-level contours*

Equal-loudness-level contours were drawn with the aid of the frequency pairs in which the reference tone was not 1000 Hz (Figs. 9—11) A comparison of the phon contours and other equal-loudness contours reveals that the contours have a similar slope as long as the reference tone has a frequency of 500 Hz or more On the other hand the equal-loudness contours drawn with 125 and 250 Hz as reference tones have a straighter course than the phon contours. Furthermore all the equal-loudness level curves show the same phenomenon as the phon curves, viz. that the monaural matching curve runs above the corresponding binaural curve

3 *Amplitude comparison between neighbouring and widely separated frequencies* Table 5 shows the average amplitudes of the two groups of frequencies. Frequency pairs 125—250 250—500 1000—2000 1000—500 2000—3000 on the one hand and 1000—8000 2000—8000 500—4000 250—4000 125—2000 on the other were selected for the mean value comparison of the excursions. Although all test subjects found it easier to compare neighbouring frequencies than those further apart no statistically demonstrable differences in the amplitude of excursions existed between the groups compared

4 *Amplitude comparison between low or high frequencies* Statistically using the arithmetic mean no significant differences were noted in the amplitude of balancing excursions of the high frequency pairs on the one hand and the low ones on the other (Table 6) Frequency pairs 4000—8000 4000—6000 3000—8000 3000—6000 3000—4000 were selected for the former and 250—500 125—2000 125—1000 125—500 125—250 for the latter group Comparison was carried out at all sensation levels.

Table 6 reveals clearly the same trend as Table 4 viz. that the amplitude of the excursions diminishes at the higher levels of comparison

Table 5 *Average amplitudes of balancing excursions (dB) with neighbouring and widely separated frequencies*

SL	Pure tone pairs with neighbouring frequencies				Pure tone pairs with widely separated frequencies			
	Monaural		Binaural		Monaural		Binaural	
	mean	SD	mean	SD	mean	SD	mean	SD
20	11 1	2.3	11 1	2.5	11 2	2.3	11 1	2.7
40	11 1	2.7	10 7	2.4	11 0	2.8	11 4	2.7
60	10.3	2.1	10 2	1 8	10 4	2.1	10.5	2.1
80	9 9	2.1	9 9	2.0	9 9	2.1	9 6	1 9
max	10 7	2.7	11 0	3 0	10 0	2.2	9 8	3 1

Table 6 *Average amplitudes of balancing excursions (dB) at high or low frequencies*

SL	High frequencies				Low frequencies			
	Monaural		Binaural		Monaural		Binaural	
	mean	SD	mean	SD	mean	SD	mean	SD
20	10 9	2.5	10.3	2.0	11.3	2.5	11.2	2 9
40	11 1	2.8	11.2	3 0	10 9	2 7	10.8	2 3
60	10.5	2 4	10 7	2.6	10.3	2.2	10 1	2 0
80	9 8	2.0	9.5	2.2	10 2	2.5	10 8	2 7
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D Matching functions between pure tones

When matching functions between pure tones were drawn from the values calculated by computer the initial point (threshold values) of the functions was taken as the arithmetic mean threshold value defined above. This was necessary because in this way the first curve of the equal-loudness-level contours drawn with the aid of matching functions became indentical with the threshold curves. The computer calculated the mean values of both frequencies for the system of coordinates with the least squares method in both directions from the centre of the curve For this reason the points at both ends of the function are partially deter mined also by the location of the points along the curve When the computer-calculated threshold values were compared with the arithmetic threshold values, the difference was found to be at the most 2—3 dB and in many cases the values were the same

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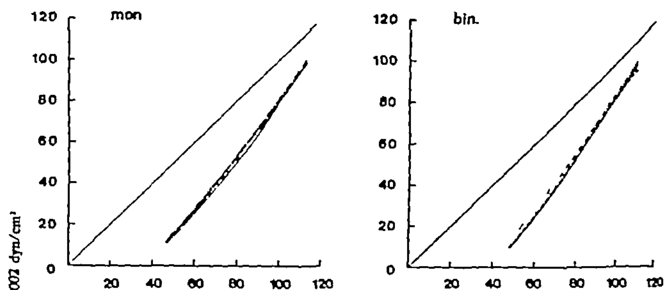
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The loudness level of a given tone in terms of phons is equal to the sound pressure level (re 0 0002 dyn/cm^2) of a *1000* Hz tone that to subjects with normal hearing sounds equally loud as the tone concerned. Phon contours were drawn with the aid of frequency pairs in which 1000 Hz was the reference tone. The threshold contour is at the same time the 0 phon contour A comparison of the mon and binaural phon contours reveals that the former needed slightly less intensity for equal loudness than the binaural test at both low and high frequencies (Fig 8)

2 Other equal-loudness-level contours

Equal-loudness-level contours were drawn with the aid of the frequency pairs in which the reference tone was not 1000 Hz (Figs. 9—11) A comparison of the phon contours and other equal loudness contours reveals that the contours have a similar slope as long as the reference tone has a frequency of 500 Hz or more On the other hand, the equal-loudness contours drawn with 125 and 250 Hz as reference tones have a straighter course than the phon contours Furthermore, all the equal-loudness level curves show the same phenomenon as the phon curves viz. that the monaural matching curve runs above the corresponding binaural curve.



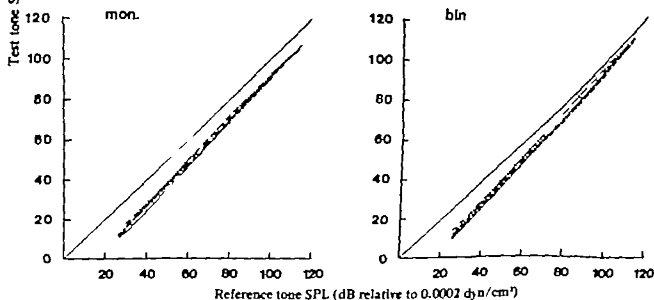
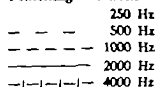
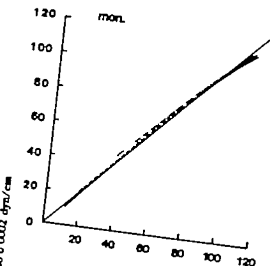
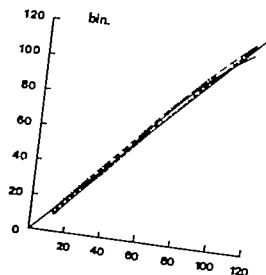


Fig 4 Matching functions

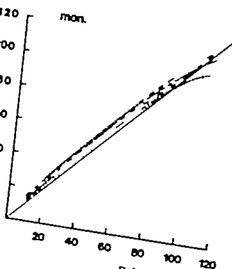


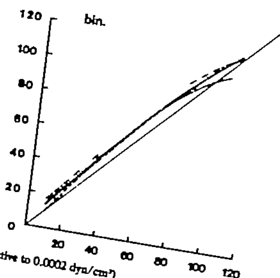
500Hz as reference tone





1000Hz as reference tone



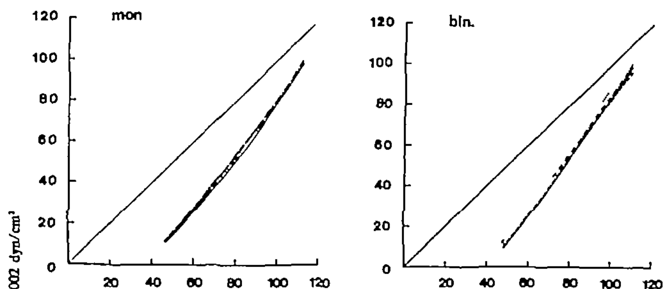


Reference tone SPL (dB relative to 0.0002 dyn/cm²)

...5. Matching functions

- — — — — 1000 Hz
- ———— 2000 Hz
- — 3000 Hz
- ⊢⊢⊢⊢ 4000 Hz
- — — 6000 Hz
- —▪—▪—▪— 8000 Hz

125 Hz as reference tone



250 Hz as reference tone

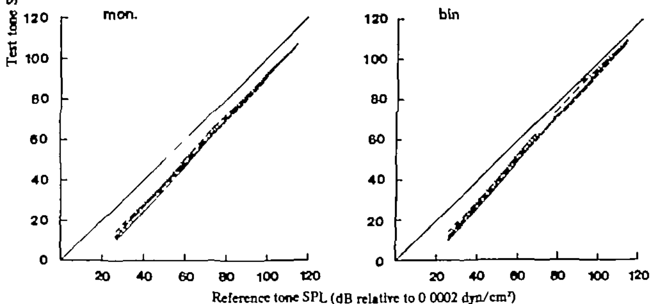
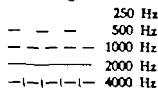
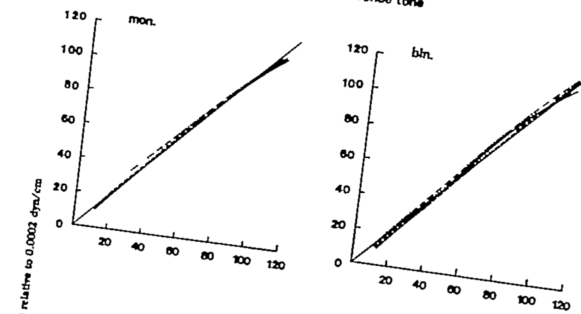


Fig 4 Matching functions



250 Hz
500 Hz
1000 Hz
2000 Hz
4000 Hz



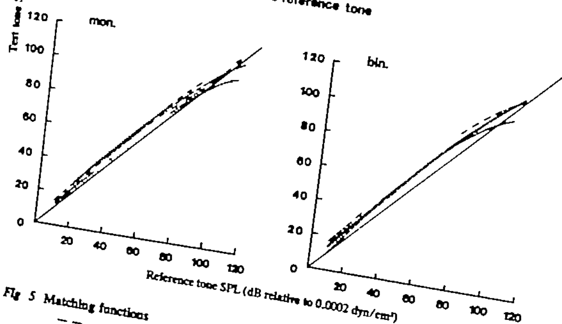
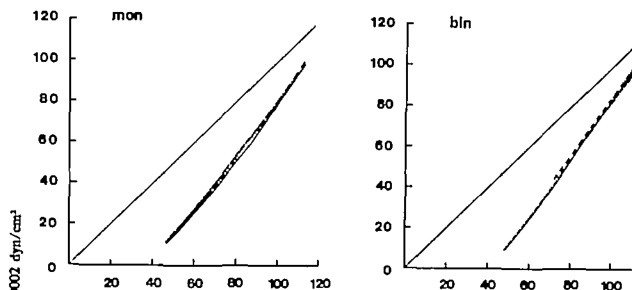


Fig 5 Matching functions

Line style	Frequency
— — — —	1000 Hz
————	2000 Hz
—	3000 Hz
|—|—|—|—|—	4000 Hz
— —	6000 Hz
—•—•—|—|—	8000 Hz



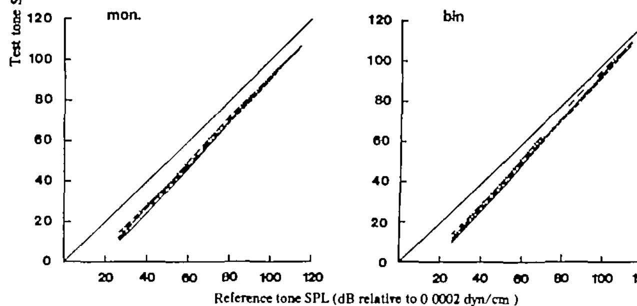
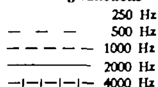
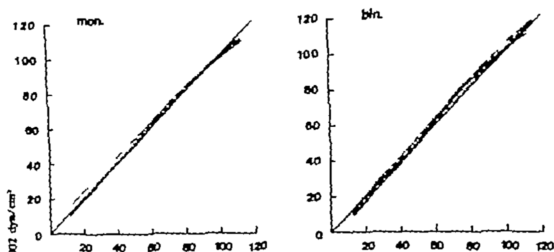


Fig 4 Matching functions



800Hz as reference tone



Test tone SPL dB relative to 0.0002 dyn/cm²

1000Hz as reference tone

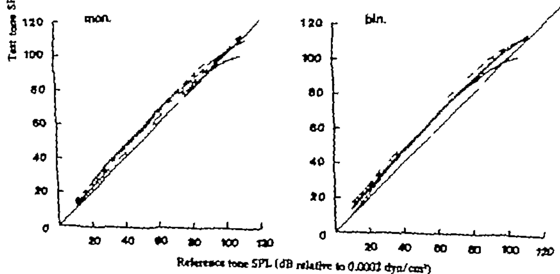
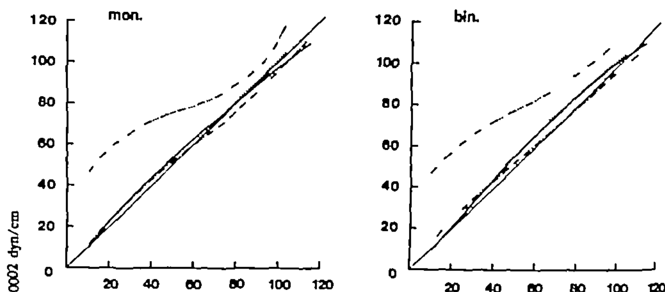


Fig 5. Matching functions

— — — — —	1000 Hz
————————	2000 Hz
—	3000 Hz
⊢⊢⊢⊢⊢	4000 Hz
— —	6000 Hz
—ı—ı—ı—ı—	8000 Hz



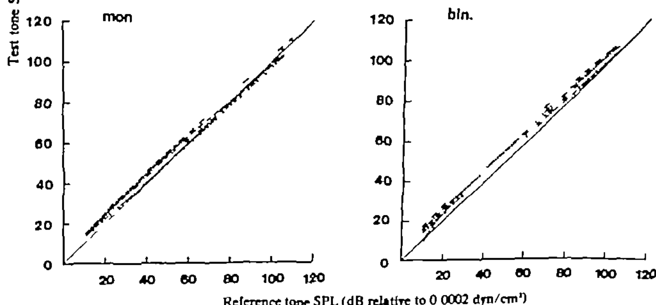
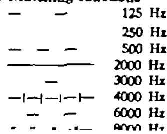
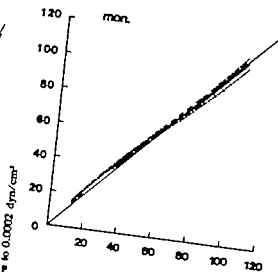
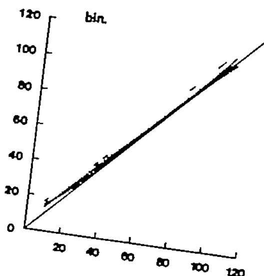


Fig 6. Matching functions

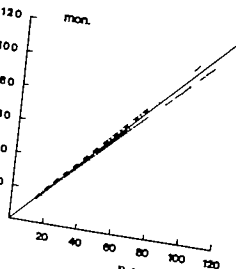


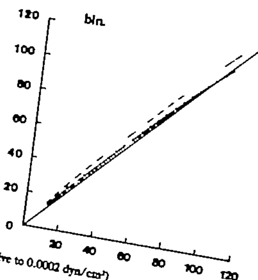
3000Hz as reference tone





4000Hz as reference tone





Reference tone SPL (dB relative to 0.0002 dyn/cm²)

7 Matching functions
—|—|—|— 4000 Hz
— — 6000 Hz
—ı—ı—ı— 8000 Hz

Table 7 *Standard deviation of the matching functions between pure tones*

Monaural test								Binaural test						
Test tone	Reference tone							Reference tone						
	4000	3000	2000	1000	500	250	125	4000	3000	2000	1000	500	250	125
8000	5 6	7 0	8 2	7.3				5 7	6 6	7.3	7 9			
6000	5 4	6 2	6 8	6 9				6 0	6 1	6.5	7.8			
4000		5 8	6 7	7 1	6 7	7 1			5 6	6.3	7 0	6 0	8 3	
3000			5 8	6 7						6 0	7 7			
2000				6 4	5 7	7.5	8 9				5 8	6 2	8.3	12.0
1000					5.3	6 2	9 3					5 7	7 2	10.5
500				6 2		6.8	9 4				6 7		7 8	11.3
250				6 7			7 8				7 4			9.5
125				6 8							8 4			

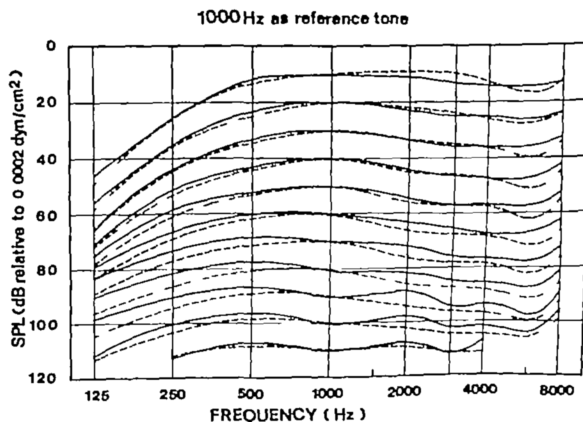


Fig 8 Phon contours Continuous lines are monaural and broken lines binaural phon contours In the succeeding figures continuous and broken lines *refer* equally to monaural and binaural study

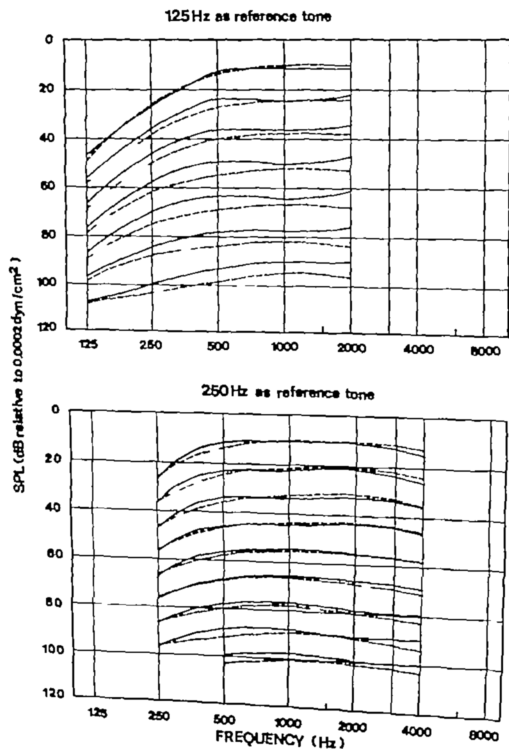


Fig 9 Equal loudness level contours

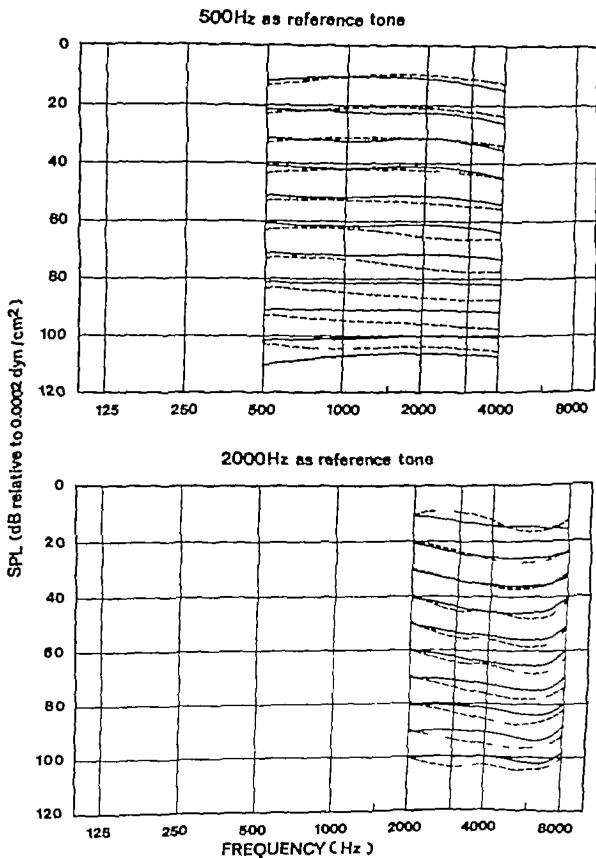


Fig 10. Egual loudness level contours

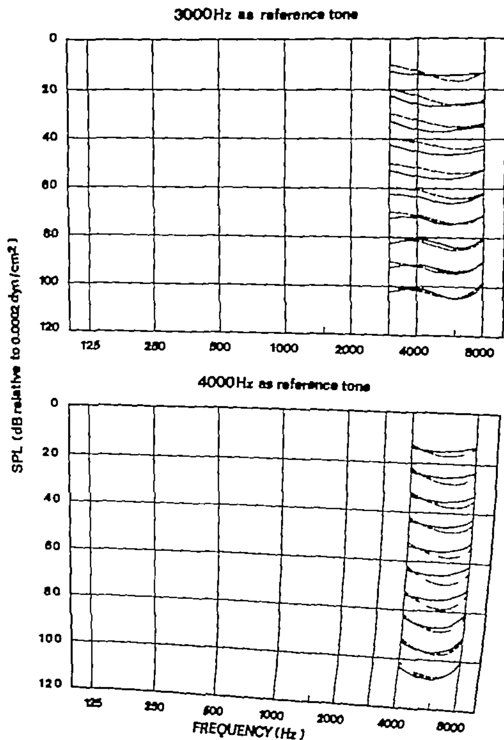


Fig. 11. Equal-loudness-level contours

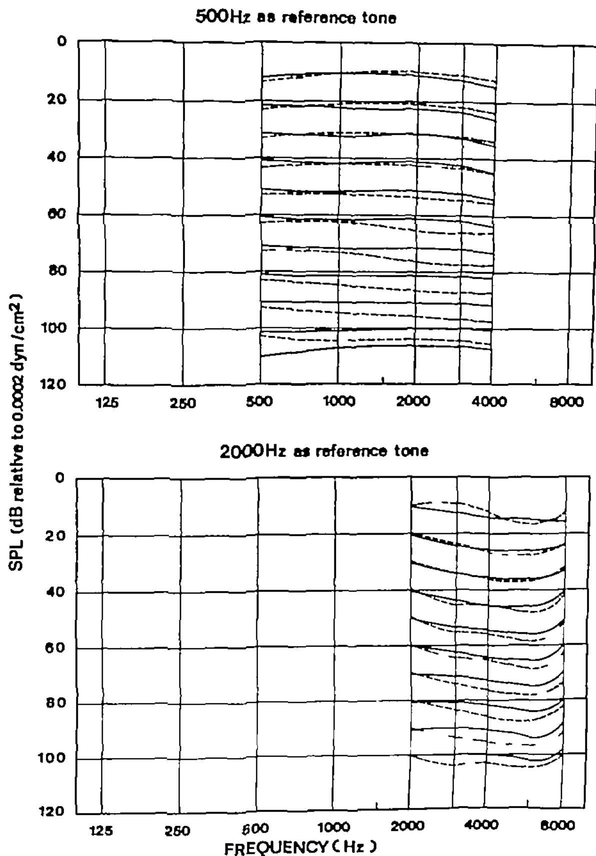


Fig 10 Egual loudness level contours

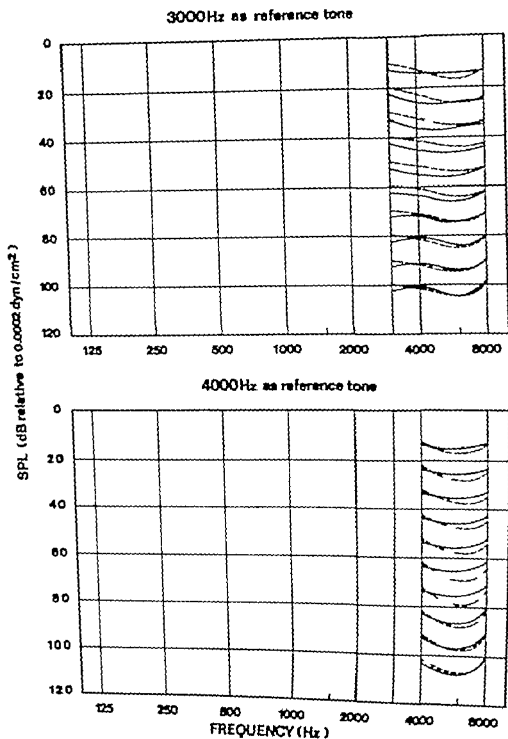
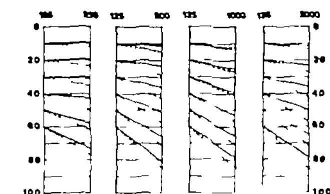


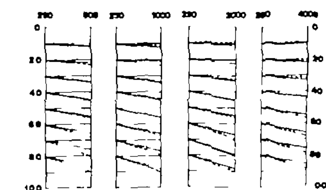
Fig. 11. Equal loudness level contours

F Scale graph

The illustrations are in principle composed in the same way as Fowler s scale graph (Figs 12—15) The graphs are so drawn that the threshold values of the two frequencies com pared are given as zero after which mutually corresponding values at 10 dB intervals have been chosen from the matching function In the columnar diagram the first frequency is the reference tone. Not all columns reach the 100 dB sensation level mainly because of the high thres-hold value of low frequencies and partly because of the inadequate power of the equipment. Com-parison of the monaural and binaural ladder grams again shows that the monaural test tone levels are higher than the corresponding binaural but the trend is similar in both com parisons

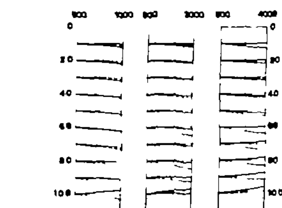


Scale graph 125 Hz as reference tone

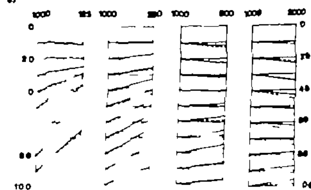


Scale graph 250 Hz as reference tone

Fig 12.

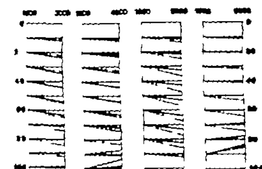


Scale graph 500 Hz as reference tone

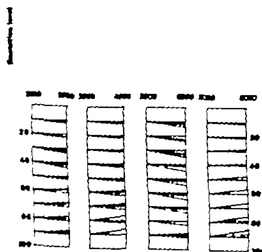


Scale graph 1000 Hz as reference tone

Fig 13

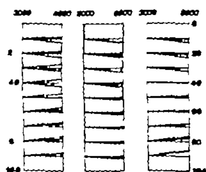


Scale graph 1000Hz as reference tone

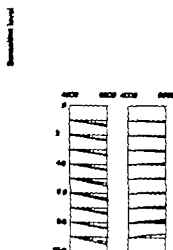


Scale graph 2000 Hz as reference tone

Fig. 14



Scale graph 3000 Hz as reference tone



Scale graph
4000Hz as reference tone

Fig. 15.

DISCUSSION

A Thresholds

The frequencies compared had the stimulus duration of 400 msec with a pause of the same length There is a complete agreement (Munson 1947 Garner 1947 Wittich 1966) that these tones are sufficiently long to reach their full loudness value The rise-decay time of the stimulus was 30 msec, a time sufficient to elimi nate "switching transients The stimuli thus were adequate for loudness level comparisons

The threshold determinations were carried out with continuous tones because of a background noise produced by the interrupter This was not considered to affect the test results as it has been shown that threshold values on normal subjects using continuous or pulsated tone are overlapping (Palva 1956 1957 Corso & Wilson 1957 Jokinen 1969) In the present series no adaptation was noted in the slope of the threshold recordings traced at a fixed frequency Abnormal adaptation to a continuous tone is so uncommon in normal subjects that it need not be expected to occur although the phenomenon must be kept in mind (Palva & Palva 1963)

The originally planned comparison levels did not hold good in detail because the measured thresholds were rounded to the nearest 5 dB This however does not affect the course of the matching function between the various pure tones. Threshold values have their individual readings for different persons and the sensation levels based on them therefore would in no case be on the same SPL readings. Ward (1966) points out that neither SL nor SPL is usually related to loudness in exactly the same way for the two ears at the same frequency or for two frequencies on the same ear

The present threshold SPL values are throughout slightly higher than the values reported from earlier equal loudness level studies An exception is made by the frequencies above 1000 Hz, on which Ross (1967) had the highest thresholds of all These differences have some bearing upon the method used for threshold testing and upon the point designated as the threshold in self recording audiometry Other differences are due to the methods of using either minimum audible field or minimum audible pressure values. This amounts to about 6 dB (British Standard 2497 1954) which is practically constant throughout the frequency range This is also in agreement with the data by Sivian & White (1933)

The mean amplitudes of the self recording automatic threshold excursions obtained at threshold vary within the range of 7 9 and 10 7 A similar result was arrived at by Palva (1957) who found that normal subjects occasionally showed amplitudes below 5 dB and the 20 dB limit was seldom exceeded In the present study the values ranged from 5 to 19 dB Jokinen (1969) also reported similar results The size of the excursions at suprathreshold comparison levels was significantly smaller at some of the levels but no frequency dependence was observed

B Matching functions between pure tones

Ross (1967) reconstructed the matching functions from the previous studies corresponding to a medium frequency (e.g. 1000 Hz) and one or two low frequencies. He stated that the matching functions from the three earlier studies showed a double inflection, and the data from Zwicker & Feldtkeller (1955) showed a slight double inflection. In the present study a third-power curve was chosen to illustrate the matching functions since it seemed to suit the practical purposes best. Trial runs of the results were carried out with higher equations, but the curves seemed to become too curly and they apparently did not reflect the true form.

A comparison showed that the differences between mon- and binaural curves (Figs. 4—7) were small. The most noticeable difference was in the pair 4000—8000 Hz in which the matching function in the monaural test lays below the basic line. The double inflection of the curves was most distinct in the monaural test, and especially at the low frequencies, below 1000 Hz. At these frequencies the asymptotic approach of the function to the 45-degree line serving as the basic line was clear. This phenomenon in normal ears is similar to Fowler's graph of the recruitment in hearing impairment and is a constant finding in all studies with loudness contour matches.

C Phon contours

Fletcher & Munson (1933) chose the threshold values so that the 0 phon contour at 1000 Hz passed through 10- W/cm² or approximately the 0.0002 dyn/cm value. The curve so obtained was 3—4 dB below the average values measured in their series. Furthermore it was seen that the contour was not uniformly below the experimental alues but approached the experimental threshold contour at the low frequencies. Nor did Churcher & King (1937) draw their 0 phon contour through the values obtained at threshold determinations (Robinson & Dadson 1956)

The threshold values or 0 phon contour obtained in the present study are closest to those obtained by Zwicker & Feldkeller (1955) At low frequencies the correlation is good, but at high frequencies the present values are c. 5 dB below those quoted in their paper although they are smaller than the values obtained by Ross (1967)

The present phon contours at low frequencies and low sound-pressure levels distinctly approached each other A phenomenon resembling recruitment emerged most clearly at 125 Hz, between 60—80 dB. A similar loudness recruitment has also been reported from earlier equal loudness determinations. With values exceeding 80 dB the phon contours were evenly spaced at 10 dB from one another

When the phon contours of the present study were compared with those of Fletcher & Munson (1933) a dissimilar course was seen at high frequencies (Fig. 16) It must be taken into account that at the high frequencies, 600—8000 Hz, sound reproduction by the receivers, however was not ideal (Fig 2) The contours obtained by latter authors had the shape of a gently curved letter U in the ascending decibel grading and those by Zwicker & Feldtkeller (1955) were similar The most remarkable difference from their curves was that the present contours turned downward at 6000 Hz. A similar result was reported by Ross (1967) At the low frequencies, the curves obtained in the present study approach each other more steeply than those reported from other studies. At high sound pressure levels the differences diminished, and the 80 phon curves were already almost parallel.

DISCUSSION

A Thresholds

The frequencies compared had the stimulus duration of 400 msec with a pause of the same length There is a complete agreement (Munson 1947 Garner 1947 Wittich 1966) that these tones are sufficiently long to reach their full loudness value The rise-decay time of the stimulus was 30 msec a time sufficient to elimi nate switching transients" The stimuli thus were adequate for loudness level comparisons

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contours revealed that they followed very similar slopes, although they were drawn for different reference tones. An exception was made by 125 Hz contours where this similarity was lacking. By and large the similarity of the contours for different reference tones is evidence of the precision and validity of the comparisons made.

The phon contours and other loudness level contours were also mutually compared, and the latter were found to have a considerably straighter course. The phenomenon reminiscent of loudness recruitment at the low end of the phon contours was clearly visible only in the contours drawn with 125 Hz as the reference tone. This straightening of the curves when low frequency was taken as the reference tone may partly be due to the greater difference limen at low frequencies, described by Riesz (1928). One indication of the somewhat less accurate loudness comparison at low frequencies was the larger standard deviation (Table 7). This is especially evident in the binaural comparison. It might then be expected that, as an indication of a less accurate comparison at low frequencies than at high, the Békésy excursions would be larger at the low frequencies. However, this was not the case (Table 6).

When one looks for the causes of the differences between the phon contours and equal loudness-level contours at low frequencies, the most obvious seems to be the greater difference limen at the low frequencies, which was mentioned above. As a result, in a loudness comparison with a low frequency as the reference tone, the variation possibilities of the test tone being judged equally loud (by the adjustment method) are greater than in the opposite case when the higher frequency is used as reference tone.

No suitable statistical means of measuring the significance of differences was found for the mutual comparison of the monaural and binaural loudness matching. Usually the monaural test needed smaller sound pressures for equal loudness with 1000 Hz tone than the corresponding binaural test. A factor possibly entering into the question might be the central components associated with the physiology of hearing. This is doubtful, however, since even the binaural test involves, in principle, monaural hearing, for the tones were given alternately and not simultaneously to both ears. Furthermore no absolute regularity was observable in the differences between the contours.

Many authors have emphasized that the comparison in Reger's test should not be carried out with frequencies more than two octaves apart (Lidén 1962). Table 5 shows, however, that there were no statistically significant differences in the amplitudes of balancing excursions between pure tones close to each other and those more than two octaves apart. This can be taken as evidence that the test subjects showed no uncertainty in their selection of the equal-loudness-level, although they found the comparison of closely spaced frequencies easier.

E Scale graph

As already mentioned, the results obtained from monaural loudness level comparison studies for demonstration of a recruitment phenomenon had to be taken from the equal-loudness level contours. Comparing is slow, but the task can be facilitated with the aid of the scale graph method developed by Fowler (1936). The equal-loudness level curves measured on normal subjects can be converted into a laddergram similar to that used for the loudness level comparisons with one frequency. This time the comparison involves two different frequencies, with the reference tone on the left vertical axis and the test tone on the right.

The illustrations on pages 32—36 have been redrawn by placing the 0 dB sensation level at the top of the scale. This presentation is used if the scale graph is drawn on ordinary audiogram paper superimposed on the audiogram. Most often, however, in ordinary clinical work the scale graph is presented with the sensation level of 0 dB at the bottom. The first connecting line between the vertical axes is obtained by connecting the threshold values together. The next lines in the laddergram are obtained in the same way as was described in the chapter

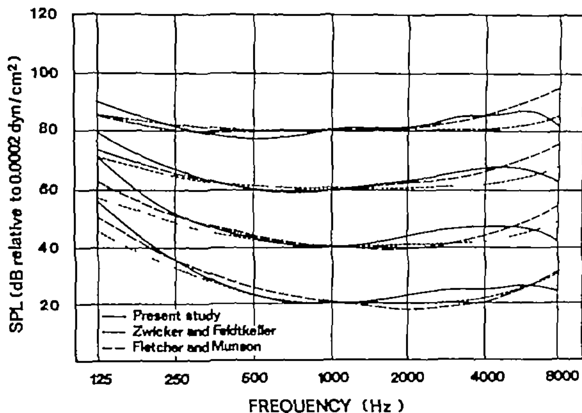


Fig 16. Comparison of three phon cotour studies

D Equal loudness level contours

The original study plan omitted 1000 Hz as a test tone when the matched pairs of pure tones were selected since the inclusion of 1000 Hz as a reference tone in the comparison was considered sufficient An analysis of the results revealed that the course of equal loudness level contours was similar to that of the binaural phon contours whereas discrepancies were noted in the monaural phon contours and other monaural equal loudness level contours. For this reason 125 250 and 500 Hz were once again compared with 1000 Hz in ten test subjects. It was found that the values obtained closely followed the previously drawn equal loudness level contours This procedure at the same time, provided conclusive evidence of the reliability of the loudness comparison test in repetitions

The monaural phon contours and other monaural equal loudness level contours showed throughout lower loudness levels than the binaural At the low end the monaural phon contours ran slightly closer to each other than the binaural These discrepancies were at first suspected to be due to a calibration error but determinations after physical checks gave values identical with those obtained in the original measurement In addition the discrepancies emerged most clearly only after 50 phons i e on the higher sound pressure levels. Also with 250 and 500 Hz as reference tone, the mon and binaural equal loudness level contours were similar

Comparison of the equal loudness level

contours revealed that they followed very similar slopes, although they were drawn for different reference tones. An exception was made by 125 Hz contours where this similarity was lacking. By and large the similarity of the contours for different reference tones is evidence of the precision and validity of the comparisons made.

The phon contours and other loudness level contours were also mutually compared, and the latter were found to have a considerably straighter course. The phenomenon reminiscent of loudness recruitment at the low end of the phon contours was clearly visible only in the contours drawn with 125 Hz as the reference tone. This straightening of the curves when low frequency was taken as the reference tone may partly be due to the greater difference limen at low frequencies, described by Riesz (1928). One indication of the somewhat less accurate loudness comparison at low frequencies was the larger standard deviation (Table 7). This is especially evident in the binaural comparison. It might then be expected that, as an indication of a less accurate comparison at low frequencies than at high, the Békésy excursions would be larger at the low frequencies. However this was not the case (Table 6).

When one looks for the causes of the differences between the phon contours and equal loudness-level contours at low frequencies, the most obvious seems to be the greater difference limen at the low frequencies which was mentioned above. As a result, in a loudness comparison with a low frequency as the reference tone the variation possibilities of the test tone being judged equally loud (by the adjustment method) are greater than in the opposite case when the higher frequency is used as reference tone.

No suitable statistical means of measuring the significance of differences was found for the mutual comparison of the monaural and binaural loudness matching. Usually the monaural test needed smaller sound pressures for equal loudness with 1000 Hz tone than the corresponding binaural test. A factor possibly entering into the question might be the central components associated with the phyiology of hearing. This is doubtful, however since even the binaural test involves, in principle, monaural hearing for the tones were given alternately and not simultaneously to both ears. Furthermore no absolute regularity was observable in the differences between the contours.

Many authors have emphasized that the comparison in Reger's test should not be carried out with frequencies more than two octaves apart (Lidén 1962). Table 5 shows, however that there were no statistically significant differences in the amplitudes of balancing excursions between pure tones close to each other and those more than two octaves apart. This can be taken as evidence that the test subjects showed no uncertainty in their selection of the equal loudness-level, although they found the comparison of closely spaced frequencies easier.

E Scale graph

As already mentioned, the results obtained from monaural loudness level comparison studies for demonstration of a recruitment phenomenon had to be taken from the equal-loudness-level contours. Comparing is slow but the task can be facilitated with the aid of the scale graph method developed by Fowler (1936). The equal-loudness level curves measured on normal subjects *can be* converted into a laddergram similar to that used for the loudness level comparisons with *one* frequency. This time the comparison involves two *different frequencies*, with the reference tone on the left vertical axis and the test tone on the right.

The illustrations on pages 32—36 have been redrawn by placing the 0 dB sensation level at the top of the scale. This presentation is used if the scale graph is drawn on ordinary audiogram paper superimposed on the audiogram. Most often however in ordinary clinical work the scale graph is presented with the sensation level *of 0 dB* at the bottom. The first connecting line between the vertical axes is obtained by connecting the threshold values *together*. The next lines in the laddergram are obtained in the same way as was described in the chapter

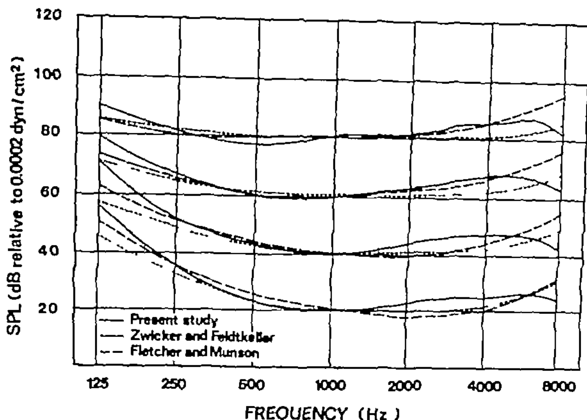


Fig 16 Comparison of three phon cotour studies

D Equal loudness level contours

The original study plan omitted 1000 Hz as a test tone when the matched pairs of pure tones were selected since the inclusion of 1000 Hz as a reference tone in the comparison was considered sufficient An analysis of the results revealed that the course of *equal loudness level contours* was similar to that of the binaural phon contours whereas discrepancies were noted in the monaural phon contours and other monaural equal loudness level contours. For this reason 125 250 and 500 Hz were once again compared with 1000 Hz in ten test subjects. It was found that the values obtained closely followed the previously drawn equal loudness level contours This procedure at the same time provided conclusive evidence of the reliability of the loudness comparison test in repetitions

The monaural phon contours and other monaural equal loudness level contours showed throughout lower loudness levels than the binaural At the low end, the monaural phon contours ran slightly closer to each other than the binaural These discrepancies were at first *suspected to be due to a calibration error* but determinations after physical checks gave values identical with those obtained in the original measurement In addition the discrepancies emerged most clearly only after 50 phons i e on *the higher sound pressure levels Also with 250* and 500 Hz as reference tone the mon and binaural equal loudness level contours were similar

Comparison of the equal-loudness level

contours revealed that they followed very similar slopes, although they were drawn for different reference tones. An exception was made by 125 Hz contours where this similarity was lacking. By and large the similarity of the contours for different reference tones is evidence of the precision and validity of the comparisons made.

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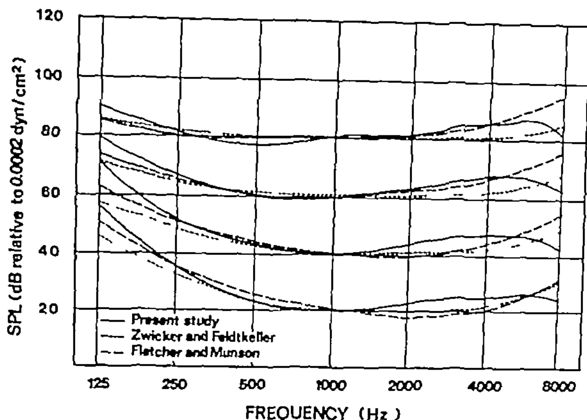


Fig 16 Comparison of three phon cotour studies

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Comparison of the equal-loudness level

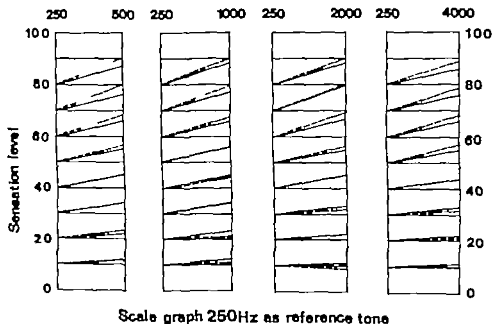

250
500
250
1000
250
2000
250
4000
100
80
60
40
20
0
Sensation level
Scale graph 250Hz as reference tone

Fig 18.

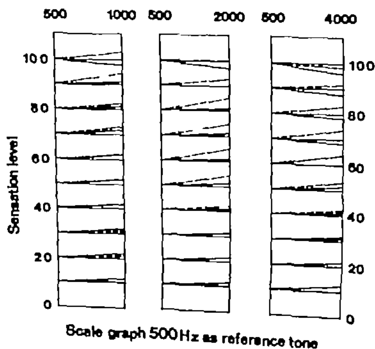

500
1000
500
2000
500
4000
100
80
60
40
20
0
Sensation level
Scale graph 500Hz as reference tone

Fig 19

dealing with Fowler s test techniques (p 5) These normal loudness level comparisons are given below to facilitate the clinical evaluation of Reger s test made of the same frequency pairs

1 125 Hz as reference tone (125—250 125—500 125—1000 and 125—2000 H)

It is seen from Fig 17 drawn with 125 Hz as the reference tone that a considerably higher sensation level is required of the test tone to attain the same loudness as the refernce tone The higher the sensation level at which the comparison is made the greater is the difference Due to the high threshold value of 125 Hz comparison could only be made at the sensation level of 60 dB due to the maximum limits of the audiometer

In both mon and binaural testing the difference was 15 dB for the pair 125—250 Hz. With the other frequency pairs the difference in the monaural test was c 20 dB and the binaural test 25 dB

2. 250 H as reference tone (250—500, 250—1000 250—2000 and 250—4000 Hz)

Fig 18 shows that at low sound-pressure levels, the same loudness is obtained at almost identical sensation levels for various test tones, but the higher the test levels chosen the more distinct become the differences At 80 dB sensation level the test tone must have an almost 10 dB higher SL to achieve the same loudness at all compared frequencies

3 500 Hz as reference tone (500—1000 500—2000 and 500—4000 Hz)

In comparison with 500 Hz as reference tone the same loudness is obtained for the three compared frequencies at approximately the same sensation levels (Fig 19) The difference is at its maximum in a monaural comparison of 500—4000 Hz. The difference however is not significant and it does not exceed 5 dB even if the SL is 100 dB

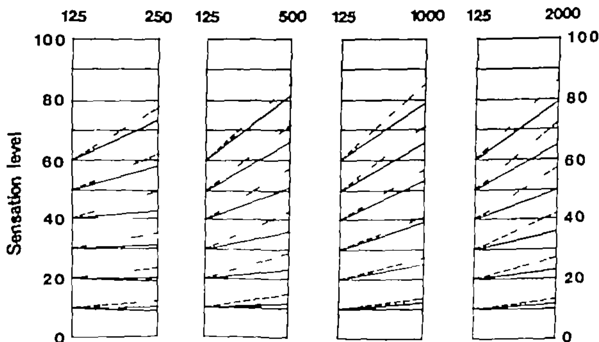


Fig 17

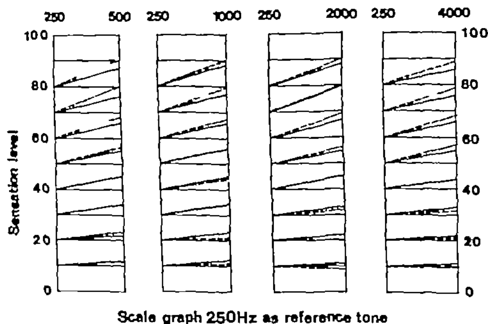

250
500
250
1000
250
2000
250
4000
Sensation level
0
20
40
60
80
100
Scale graph 250Hz as reference tone

Fig 18.

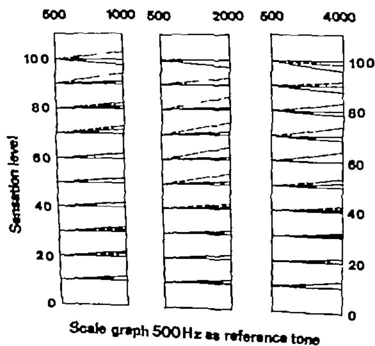

500
1000
500
2000
500
4000
Sensation level
0
20
40
60
80
100
Scale graph 500Hz as reference tone

Fig 19

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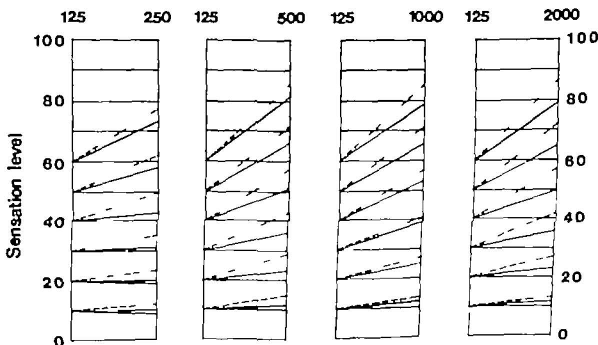


Fig 17

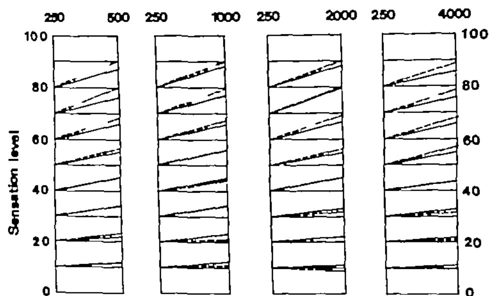

250
500
250
1000
250
2000
250
4000
100
80
60
40
20
0
Sensation level
Scale graph 250Hz as reference tone

Fig 18.

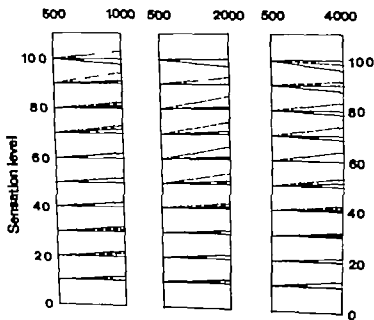

500
1000
500
2000
500
4000
100
80
60
40
20
0
Sensation level
Scale graph 500Hz as reference tone

Fig 19

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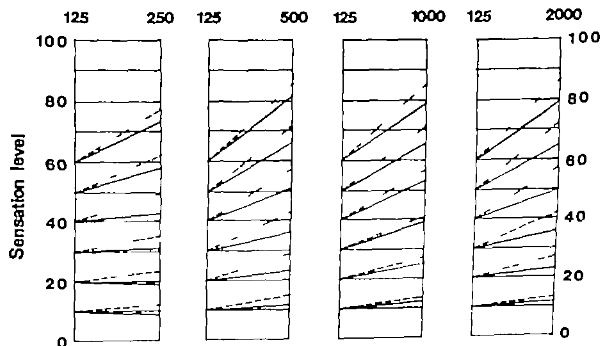


Fig 17

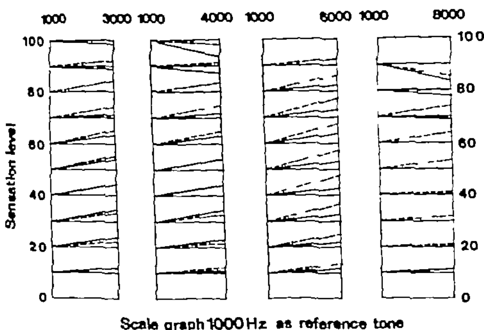

1000
3000
1000
4000
1000
6000
1000
8000
Sensation level
100
80
60
40
20
0
Scale graph 1000 Hz as reference tone

Fig 21

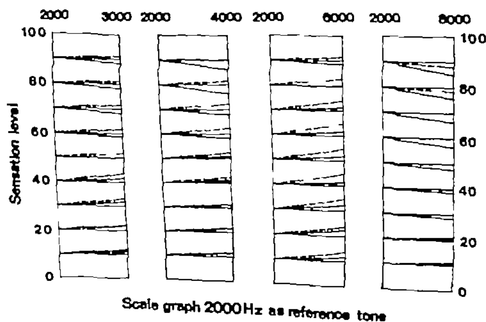

2000
3000
2000
4000
2000
6000
2000
8000
Sensation level
100
80
60
40
20
0
Scale graph 2000 Hz as reference tone

Fig 22

4 1000 Hz as reference tone (1000—125 1000—250 1000—500 1000—2000 1000—3000 1000—4000 1000—6000 and 1000—8000 Hz)

Scale graphs obtained for the test pairs 1000—125 and 1000—250 Hz are in principle similar to those for 125—1000 and 250—1000 Hz except that the direction of the connecting lines is reversed while the differences between sensation levels are of the same order of magnitude (Fig 20)

For the frequency pairs 1000—500 1000—2000 (Fig 20) 1000—3000 and 1000—6000 Hz (Fig 21) the same loudness is obtained at practically identical sensation levels In frequency pairs 1000—4000 and 1000—8000 Hz on the other hand the test tone has an SL more than 5 dB lower than that of the reference tone when tracing near the maximum limits of the audiometer in the monaural study (Fig 21) In the binaural test the difference is not so distinct

5 2000 Hz as reference tone (2000—3000, 2000—4000 2000—6000 and 2000—8000 Hz)

No test pair of the scale graphs drawn with 2000 Hz as reference tone shows a difference exceeding 5 dB between sensation levels giving the same loudness levels (Fig 22) Thus identical sensation levels give the same loudness levels with an accuracy adequate for clinical work

6 3000 Hz as reference tone (3000—4000 3000—6000 and 3000—8000 Hz)

3000 Hz as reference tone also gives equal loudness levels as the above test tones at approximately the same sensation levels (Fig 23)

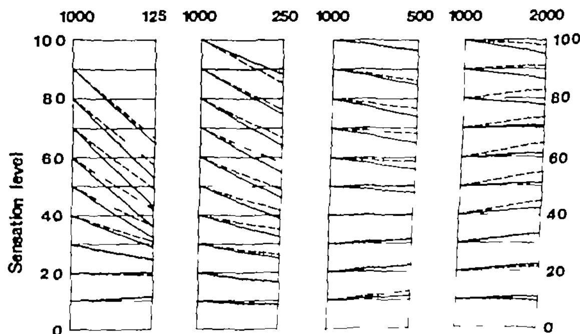
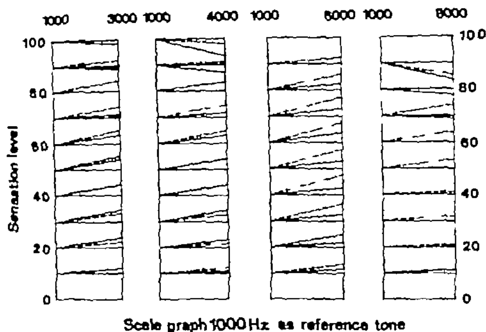
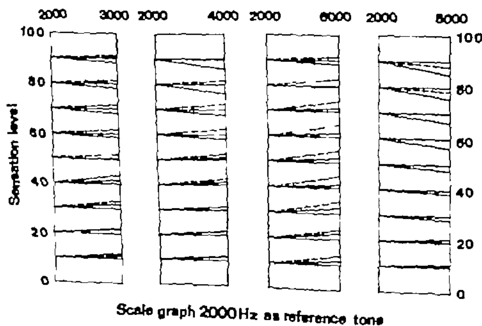


Fig 20



1000
3000
1000
4000
1000
6000
1000
8000
100
80
60
40
20
0
Sensation level
Scale graph 1000 Hz as reference tone

Fig 21



2000
3000
2000
4000
2000
6000
2000
8000
100
80
60
40
20
0
Sensation level
Scale graph 2000 Hz as reference tone

Fig 22

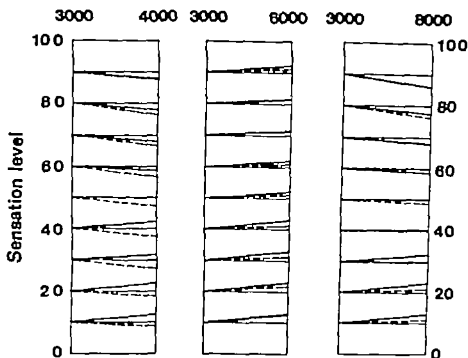

3000
4000
3000
6000
3000
8000
Sensation level
100
80
60
40
20
0
Scale graph 3000Hz as reference tone

Fig 23

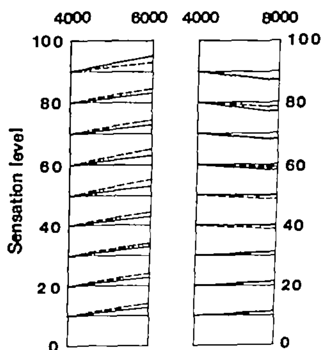
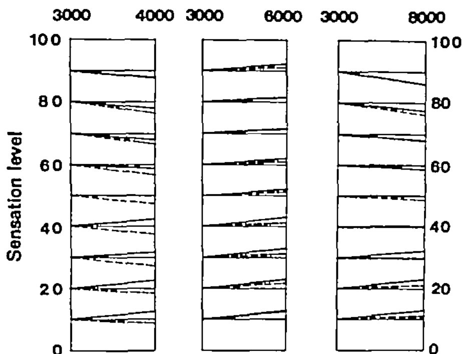

4000
6000
4000
8000
Sensation level
100
80
60
40
20
0
Scale graph
4000Hz as reference tone

Fig 24

7 4000 Hz as reference tone (4000—6000 and 4000—8000 Hz)

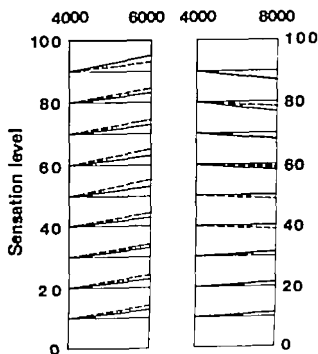
The sensation levels of the reference and test tones do not differ by more than 5 dB, and in clinical work, with a view to Reger's test, identical loudness is normally obtained at the same sensation level (Fig. 24)

As seen from the various scale graphs on normal subjects, a number of the frequencies compared gave identical loudness levels at the same sensation level Some low frequencies however gave the same loudness level even at considerably different sensation levels and for these frequencies the clinician should compare the Reger test results with those obtained on normal subjects.



3000
4000
3000
6000
3000
8000
100
80
60
40
20
0
Sensation level
Scale graph 3000Hz as reference tone

Fig 23



4000
6000
4000
8000
100
80
60
40
20
0
Sensation level
Scale graph
4000Hz as reference tone

Fig 24

could not be used alternatively in the loudness comparison, since the results obtained differed significantly ($p \leq 0.01$) With 1000 Hz as the reference tone there a greater difference in sound intensity before equal loudness was reached. The only exception was made by the pair 125—1000 Hz and 1000—125 Hz in the binaural comparison, no statistical differences were elicited between them ($p \leq 0.01$)

In the pair 125—250 Hz the test tone at the 60 dB sensation level, had to have a 15 dB higher sensation level for equal loudness to be achieved. In pairs 125—500 125—1000 and 125—2000 Hz the difference was 20—25 dB respectively

In pairs 250—500 250—1000 250—2000 and 250—4000 Hz at the sensation level of 80 dB the difference was almost 10 dB

Loudness comparison with binaural techniques revealed that the test tone required a higher intensity than in the monaural test to reach the same loudness. No cause to account for this phenomenon could be traced.

CONCLUSIONS

In the comparison of loudness levels at different frequencies with automatic testing the technique is somewhat more demanding than with the other comparison methods and a few subjects had real difficulties in the test However only one showed such inconsistency that he could not be used in the series In measurements carried out on the reported series of 14 test subjects the threshold excursions of the Békésy audiogram ranged from 5 to 19 dB The mean values of these excursions for different frequencies were within the range of 7 9—10 7 dB At the suprathreshold levels the excursions became significantly smaller at higher (60 and 80) SLs but were independent of the compared frequencies.

Reger s test can well be carried out using *automatic test techniques for frequencies* differing by more than two octaves. all test subjects in the series managed the comparison of all frequency pairs without much difficulty Statistically (Table 5) no significant differences could be found in the amplitudes of the balancing excursions in frequency pairs close to one another and those widely separated.

The phon contours obtained with automatic technique in the present study differed from those of Fletcher & Munson (1933) which in the ascending scale have the shape of a gently curved letter U whereas those of the present study turned downward at 6000 Hz. A similar difference was also reported by Ross (1967)

At low frequencies the present study disclosed a loudness recruitment similar to that described by Fletcher & Munson (1933) but at the high frequencies all phon contours were spaced by 1 dB from one another

The equal loudness level contours were almost identical although they were drawn for different reference tones. Comparison showed that equal loudness level contours had a straighter course than phon contours and the loudness recruitment at low frequencies did not emerge in them so clearly as in the phon curves An exception was made by the contours drawn with 125 Hz as reference tone.

Comparison of the Reger test results with the equal loudness level contours obtained on normal subjects takes less time when the values obtained are compared with normal values drawn directly into the scale graph form

500 2000 3000 and 4000 Hz as reference tones gave practically the same loudness as their test tones used in the comparison at the same sensation levels. The same is true of frequency pairs 1000—500 1000—2000 1000—3000 and 1000—6000 Hz.

In frequency pairs 1000—4000 and 1000—8000 Hz the test tone in the monaural test had a sensation level more than 5 dB lower than the reference tone when the audiometer was employed at its maximum limits.

Comparison with frequency pairs 1000—125 and 1000—250 Hz gave in principle the same result as 125—1000 and 250—1000 Hz, the scale graph columns presenting a mirror image However the frequency pairs of 125—1000 Hz and 1000—125 Hz on the one hand and 250—1000 Hz and 1000—250 Hz on the other

ACKNOWLEDGEMENTS

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I also wish to thank Mr Jorma Pietilä who carried out the statistical analysis of the study results, and Mr Heikki Nieminen and Mrs Seija Nieminen who prepared the numerous pictures. My warm thanks should also go to Mrs Hilkka Kontiopää, M.A for translating the Finnish manuscript, to Mrs Barbara Rikberg for checking the English, and also to Mrs Pirkko Orell for collecting the literature

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Oulu, June 1974

Seppo Karjalainen

SUMMARY

The purpose of the study was to compare with the aid of automatic testing techniques the loudness levels of different frequencies of pure tones, both monaurally and binaurally The risk that the comparison made by the test subject might be affected by the researcher was thus reduced to a minimum and the phon contours obtained in this way were compared with those obtained by using manual techniques. An attempt was made to facilitate the clinician s work by converting the equal loudness level contours into scale graphs with which the Reger test results can be compared in order to establish quickly whether loudness recruitment is present

The series consisted of 14 test subjects who compared tones heard through earphones at sensation levels of 20 40 60 and 80 dB finally extending the comparison to the maxi mum limits of the Békésy audiometer Holding a push button in his hand, the test subject regulated the test tone to follow the loudness of the reference tone

The comparison covered nine frequencies from the 125—8000 Hz range and a total of 28 test pairs were matched In this way almost all frequencies served in the comparison both as reference and as test tones The duration of sound impulses was 400 msec and rise decay time was 30 msec The interval between pulses was 400 msec. The time available for balancing per test pair was 1 minute

A mean value curve was calculated from the threshold measurements The two ears displayed an equal hearing ability at low frequencies up to 1000 Hz but at high frequencies the left ear was slightly better The difference was over 3 dB at its maximum at 3000 Hz, but it was not signifi cant In threshold determinations the ampli tudes of excursions ranged from 5 to 19 dB and were slightly greater at low frequencies but no significant differences appeared

The amplitudes of balancing excursions tended to diminish at high comparison levels and the difference was significant in the monaural study between levels 20 and 60 20 and 80 dB and 20 and the maximal sensation level In the binaural study the difference was signi ficant between sensation levels 20 and 60 and 20 and 80 dB

The test subjects made the comparison accurately also at frequencies two octaves apart although it was found easier to match fre quencies that were closer to each other In the mon and binaural method of comparison the differences between the results or testing tech niques were not significant.

The phon contours obtained were similar to those of Fletcher & Munson (1933) at low frequencies but had a different course at high frequencies The difference was greatest at 6000 Hz where the Fletcher and Munson contours of the ascending scale were U shaped The contours obtained in the present study curved downwards at 6000 Hz.

The equal loudness level contours obtained were finally presented in the form of scale graphs A reduction of the initial loudness level differences normally took place in frequency pairs in which one of the two test frequencies was 125 or 250 Hz. Of the high frequency pairs balancing occurred with a sensation level difference exceeding 5 dB only at 1000—4000 Hz and 1000—8000 Hz. By comparing the Reger test results with the presented scale graphs the possible recruitment in cases of hearing impair ment can be quickly established, and is not confused with the physiological loudness rec- ruitment between frequencies

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Oulu, June 1974

Seppo Karjalainen

SUMMARY

The purpose of the study was to compare with the aid of automatic testing techniques, the loudness levels of different frequencies of pure tones both monaurally and binaurally The risk that the comparison made by the test subject might be affected by the researcher was thus reduced to a minimum and the phon contours obtained in this way were compared with those obtained by using manual techniques An attempt was made to facilitate the clinician s work by converting the equal loudness level contours into scale graphs with which the Reger test results can be compared in order to establish quickly whether loudness recruitment is present

The series consisted of 14 test subjects who compared tones heard through earphones at sensation levels of 20 40 60 and 80 dB finally extending the comparison to the maxi mum limits of the Békésy audiometer Holding a push button in his hand the test subject regulated the test tone to follow the loudness of the reference tone

The comparison covered nine frequencies from the 125—8000 Hz range and a total of 28 test pairs were matched In this way almost all frequencies served in the comparison both as reference and as test tones The duration of sound impulses was 400 msec and rise decay time was 30 msec The interval between pulses was 400 msec The time available for balancing per test pair was 1 minute

A mean value curve was calculated from the threshold measurements The two ears displayed an equal hearing ability at low frequencies up to 1000 Hz but at high frequencies the left ear was slightly better The difference was over 3 dB at its maximum at 3000 Hz, but it was not signifi cant In threshold determinations the ampli tudes of excursions ranged from 5 to 19 dB and were slightly greater at low frequencies, but no significant differences appeared

The amplitudes of balancing excursions tended to diminish at high comparison levels and the difference was significant in the monaural study between levels 20 and 60 20 and 80 dB and 20 and the maximal sensation level In the binaural study the difference was signi ficant between sensation levels 20 and 60 and 20 and 80 dB

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The phon contours obtained were similar to those of Fletcher & Munson (1933) at low frequencies but had a different course at high frequencies The difference was greatest at 6000 Hz where the Fletcher and Munson contours of the ascending scale were U-shaped The contours obtained in the present study curved downwards at 6000 Hz.

The equal loudness level contours obtained were finally presented in the form of scale graphs. A reduction of the initial loudness level differences normally took place in frequency pairs in which one of the two test frequencies was 125 or 250 Hz. Of the high frequency pairs balancing occurred with a sensation level difference exceeding 5 dB only at 1000—4000 Hz and 1000—8000 Hz. By comparing the Reger test results with the presented scale graphs the possible recruitment in cases of hearing impair ment can be quickly established and is not confused with the physiological loudness rec ruitment between frequencies.

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Correlative Studies on the Cochlear Pathology and Hearing Loss in Guinea-pigs after Intoxication with Ototoxic Antibiotics

BY
JUKKA YLIKOSKI
in cooperation with
JAN WERSÄLL and BIRGITTA BJÖRKROTH

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SUPPLEMENTUM

Correlative Studies on the Cochlear Pathology and Hearing Loss in Guinea-pigs after Intoxication with Ototoxic Antibiotics

BY

Jukka Ylikoski

in cooperation with Jan Wersäll and Birgitta Björkroth

From The King Gustaf V Research Institute, Stockholm, Sweden,
The Department of Otolaryngology University Hospital of Helsinki, Finland and
The Department of Otolaryngology Huddinge Sjukhus, Huddinge Sweden

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Contents

GUINEA-PIG HAIR CELL PATHOLOGY FROM OTOTOXIC ANTIBIOTICS

J Ylikoski

The selective ototoxic effect of certain aminoglycoside antibiotics has made them a useful tool for experimental pathology studies dealing with the organ of Corti. Since the earliest reports by Hinshaw and Feldman (1945) of ototoxic effects of streptomycin on the vestibular system, abundant data have accumulated regarding the quantitative and qualitative effect of these drugs upon the inner ear Today there are generally accepted concepts about the ototoxic potency of individual antibiotics and about the general pattern of damage upon the vestibular system and the organ of Corti. There are, however some great differences within species and among individual animals in the susceptibility to ototoxic agents. This is why rather large series of animals are necessary before general conclusions can be made. The commonly used method of decalcifying, serial sectioning and graphically reconstructing the organ of Corti (Guild, 1921 Schuknecht, 1953a) lacks accuracy when compared with the surface preparation technique (Retzius, 1884 Neubert, *1950* Engström et al. 1966). There are however very few studies where the surface preparation technique was used to evaluate the damage pattern in the organ of Corti after ototoxic antibiotics in a large number of experimental animals (Kohonen, 1965 Engström et al. 1966) Even in these studies hair cells within the entire cochlea were not counted. Instead one-third of each turn was presented as representative of the whole coil, thus these studies must be regarded as being purely qualitative in nature.

The material for the present investigation has been reported in part in a study where physiological and histological impairment in the inner ear of guinea-pigs was compared before and after treatment with various ototoxic antibiotics (Ylikoski, 1974 a) A large number of experimental animals was used for that study and a systematic quantitative registration of the cellular damage of almost the entire cochlea was made. In the present work a larger material has been further analysed light and electron microscopically with the aim of presenting systematically the cochlear damage pattern after treatment with three ototoxic aminoglycoside antibiotics, gentamicin kanamycin and neomycin.

MATERIAL AND METHODS

Eighty four healthy young pigmented guinea-pigs with normal pinnareflex, each weighing between 250–450 g, were studied. The hearing of most of the animals was audiometrically measured (Anderson & Wedenberg, 1965) as part of an earlier study (Ylikoski, 1974 a) dealing with audiological and morphological changes induced by ototoxic antibiotics. The left ear was then destroyed by surgical ablation prior to treatment with antibiotics in those animals which had been submitted to audiological examination. Gentamicin, kanamycin or neomycin were administered by subcutaneous injections twice daily in varying doses and for varying durations of time. The schedule for dosages and survival times for the 68 animals which survived treatment is given in Table I As seen in that table the animals were allowed to survive for various lengths of time after the last injection. A large number of normal guinea-pigs studied in our laboratory served as controls. All animals were decapitated while in deep chloroform anaesthesia, the temporal bones were removed

GUINEA PIG	DRUG	DOSE/day	DURATION OF TREATMENT	SURVIVAL TIME
G2 G3	Gentamicin	50mg/kg	14 days	0 days
G1 G4 G5			18–21	0–3
G6 G7 G8			14	11 13
G14 G15 G16 G17 G18 G19			29	16 30
G9 G10 G11 G12 G13		150mg/kg	6	10–13
GA2 GA3 GA4 GA12 GA13		100mg/kg	9 10	0–3
GA6 GA8 GA16			11 14	0–1
GA14 G28 G34			10 14	16–98
G23 G24 G26 G33 G35			16–17	14 210
G21 G22			21	28 43
K18	Kanamycin	200mg/kg	11	4
K19 K21 K22 K23 K24			16	30–112
K14 K15			20	27 64
K1 K3 K4 K6		300mg/kg	11 12	0–4
K8 K9 K10 K11		400mg/kg	6	6–15
K12 K13			6–7	135 180
NA2 NA3 NA8	Neomycin	250mg/kg	7 8	0–2
N14 K15			5	119–300
N3 N4 N10 N11 N13			7	39–122
N5 N6 N7			8	70–91

Table 1 *The dosage schedule and survival times of 68 guinea-pigs in which cochlear pathology was studied.*

and the cochlea was fixed in 1 % or 2 % veronal buffered osmium tetroxide and em bedded in Epon Each cochlea was divided with a thin saw through the modiolar axis and each half was split with a razor blade in such a way that each block contained the intact cochlear duct of one-half coil. The specimens were thinned and mounted on a glass slide basal membrane downwards (Ernstsson 1971) Each specimen was stud ied through a water lens 40x with a Zeiss photomicroscope equipped with the inter ference contrast optical system (Nomarski 1955) Each hair cell was counted and marked in a cytocochleogram as present or missing according to Engström et al. (1964) and Engström et al. (1966) An average cochleogram was prepared in which groups of five cells in the same row were counted When three or more were missing the hair cell group was marked as missing (Ylikoski et al 1973) otherwise as present" From the cytocochleogram the percentages of missing outer hair cells (OHCs) and inner hair cells (IHCs) respectively in each millimetre along the cochlear duct were counted and marked in the chart

Selected regions were reoriented and remounted in Epon and used for 0 5–1 micron thick sections for light microscopy and for thin sections which were studied in Siemens Elmiscope I transmission electron microscope after staining with uranyl acet ate and lead citrate (Karnovsky 1961 Watson 1958)

A few of the cochleas were opened widely after fixation rinsed in Ringer s solution frozen in liquid propane at – 192 C and freeze-dried in vacuo The specimens were plated with gold by vac-

uum evaporation and investigated with a Cambridge Stereoscan scanning electron microscope.

RESULTS

Light microscopy

Generally each of these three antibiotics produced a similar pattern of degeneration. This always initiated as a swelling and deformation of the cell bodies and the nuclei in the first row of OHCs. When degeneration progressed the cells of this row disappeared in the basal coil and the damage spread radially to other OHC rows and spirally towards the apex.

In order to present the results of the cytoarchitectural study of the cellular destruction of the organ of Corti, the animals are grouped according to the doses of antibiotics administered and to the extent of damage produced.

Gentamicin

A) Gentamicin given 50 mg/kg for from 14 to 29 days or 150 mg/kg for 6 or 7 days. This group of 19 animals was further subdivided into the following subgroups.
   1) No significant damage in the cytocochleogram (less than 1 % degenerated cells in each millimetre of the cochlea). This group consisted of five animals G 2, G 3 G 6 G 11 and G 13 (Fig. 1)

Fotnote All the dosages and total doses are given in amounts related to antibiotic base.

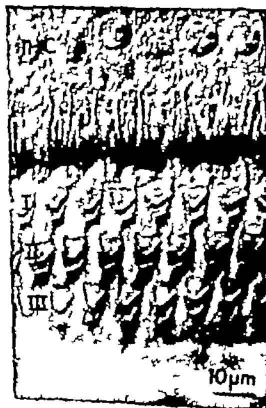


Fig. 1 Interference-contrast micrograph of the lower part of the basal coil of guinea-pig NA 2, given [illegible] 250 mg/kg for 7 days and decapitated on the 7th day. The hair cell population in this cochlea was normal.



Fig. 2. Interference-contrast micrograph of a portion of the basal coil of G 12, given gentamicin 150 mg/kg for 7 days. Some cells in the first row of OHCs have collapsed.

2) Spotty degeneration distributed over the whole cochlea (*less than 10 % missing sensory cells in each millimetre*) Five animals G 10 G 12, G 14 G 15 and G 16 (Fig 2)

3) *Moderate degeneration of the OHCs.* Nine animals belonged to this group G 1 G 4 G 5 G 7 G 8 G 9 G 17 G 18 and G 19 The most severe changes were usually seen in two areas in the hook region (round window area) and in the upper basal coil. The extent of injury varied in this group from about 50 % loss of the first row of the OHCs to an almost total loss of the OHCs in the regions named. The average loss of the OHCs of *this group is seen in Fig. 3*

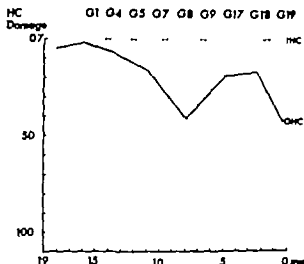


Fig. 3 Extent of mean OHC damage in 9 guinea-pigs treated with gentamicin 50 mg/kg for from 14 to 29 days as determined from the average percentage per millimetre of degenerated OHCs in each examined segment along the organ of Corti. The areas most vulnerable to degeneration are the hook region and the upper part of the basal coil. The IHCs were intact.

B) Gentamicin given 100 mg/kg for from 9 to 21 days, 18 animals.
Characteristic of this group was a great difference in damage between the three subgroups of animals.

1) Slight or no damage six animals G 22 GA 2 GA 3 GA 4 GA 12 and GA 13 One animal G 22 (Fig. 4) although given this dose for 21 days showed changes similar to those often observed in the form group treated with *50 mg/kg for* shorter period of time. The rest c this group were treated for 9 c 10 days and decapitated on th *day of the last injection. The* displayed only a subtle loss of th OHCs distributed over the entir cochlea.

2) Moderately severe degeneratio with complete loss of the OHCs i the basal half of the cochlea an varying damage to the IHCs. Thi group included 10 animals G 21 G 24 G 26, G 28 G 33 G 35 G/ 6 GA 8 GA 14 and GA 16 Th damage pattern of the OHCs (Fig 5) was rather uniform starting ba *sally as a complete loss of the cell*

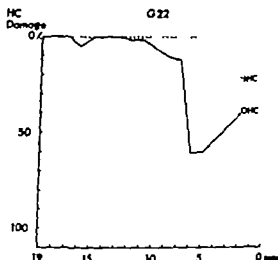
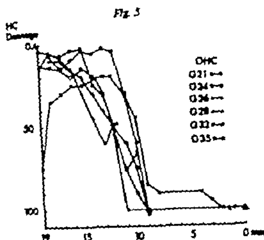
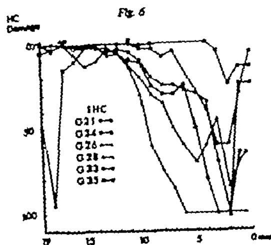


Fig. 4 Extent of hair cell damage in guinea-pig, G 22, given gentamicin 100 mg/kg for 21 days. Despite the large dosage damage was moderate.

in all three outer rows. Collapsed hair cells were replaced by the phalangeal processes of the support ing cells thus the reticular membrane was still intact. The first hair cells to appear along the basilar membrane were always in the third row these being the most resistant to ototoxic damage They appeared on the average at the 10 mm level. The second row appeared generally 1 mm higher and finally the cells of the first row commonly rem-ined





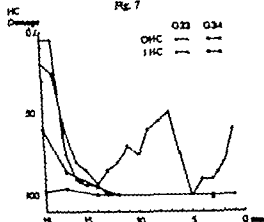


Fig. 5. The extent of OHC damage in 6 guinea-pigs given gentamicin 100 mg/kg for from 10 to 21 days was fairly uniform. All the animals suffered complete loss of OHCs in the basal cochlea. The transition from total degeneration to nearly normal configuration of OHCs occurred an average of 10 to 13 mm from the round window

Fig. 6. Extent of IHC damage in the same animals as in Fig. 5. Large variations are apparent. Early signs of damage to IHCs at the apex were noted in only one guinea-pig treated with gentamicin.

Fig. 7 Extent of OHC and IHC damage in 2 animals given gentamicin 100 mg/kg for 16 (G 23) and 14 days (G 34). Sensory cells were severely damaged in both cochleas.

from the 13 mm position upwards. The extent of damage to the IHCs varied from an intact pattern to total loss within several millimetres (Fig. 6) When all IHCs had disappeared the nerve density in the spiral osseous lamina was clearly reduced but appeared normal if the IHCs were present. In cases of advanced IHC damage the distance between the appearance of normal IHCs and the presence of near normal numbers of OHCs averaged 8 mm In this material there was only one animal given gentamicin which displayed a significant degeneration of apical IHCs in the 17–19 mm region. OHCs in this area appeared near normal and other cochlear regions displayed the typical degeneration pattern in the basal and middle turns for this group

3) Severe hair cell loss. Two animals G 23 and G 34 (Fig. 7). All the OHCs were missing except the apical 17–19 mm region where some of them were present in the second and third row The IHCs had also nearly totally disappeared. The organ of Corti collapsed in some places in the basal and second coils but pillar cells generally remained in the upper coils in spite of a complete disappearance of sensory elements in that region of the cochlea.

2) Spotty degeneration distributed over the whole cochlea (less than 10 % missing sensory cells in each millimetre) Five animals G 10 G 12, G 14 G 15 and G 16 (Fig 2)
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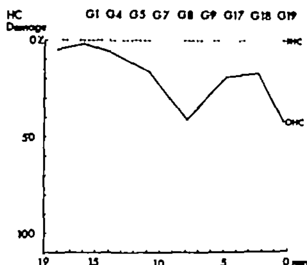


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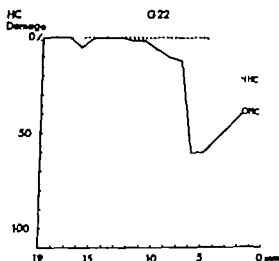


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loss of the OHCs and of the IHCs are presented, these animals displayed severe degeneration of the OHCs. The IHCs were also severely injured in varying degrees. The peculiar capacity of neomycin to produce apical IHC damage was seen in most of these animals.

Electron microscopy

Electron microscopy (EM) often revealed early degenerative changes in the sensory cells while these still appeared normal under a light microscope. There were considerable differences in EM findings between animals decapitated a few days after the last injection and animals which survived one month or more after cessation of treatment. Thus the latter group displayed fewer ultrastructural changes, and the degeneration detected by a light microscope coincided closely with EM-findings. There were no noteworthy ultrastructural differences in animals treated with gentamicin, kanamycin or neomycin provided the pattern of degeneration was similar

In animals with severe OHC degeneration in the basal coil early ultrastructural changes were usually seen in OHCs throughout the cochlea. The earliest changes included an increase in dark bodies unde the cuticular plate. Some of these particles were spherical with variable elec tron density Others were lamellated and some of them were undoubtedly degenerated mitochondria, some were apparently lysosomes. In some cells a fibrous material appeared in the supranuclear part of the cell (Fig. 18)

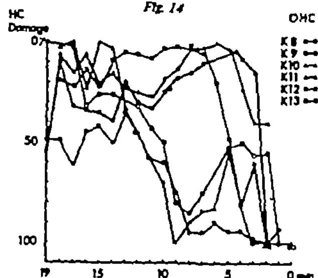
The regular arrangement of fenestrated membranes along the sides of the cell was often disrupted in the early stage of degeneration. These membranes appeared disar ranged in the cytoplasm and showed areas of condensation and rarefaction along the cell membrane. Such irregularities can normally be found in apical areas of the cochlea, but usually not in the lower turns.

A decrease in the ribosome content of the cell was a later finding often coinciding with a widening of interspaces between the layers of the fenestrated membranes along the sides of the OHCs. Vacuolization near the sides of the cells was noted and at the same time an increased number of vesicle granules appeared in the cytoplasm (and in some cells in the nucleus) Later the plasma membrane ruptured at several sites and the cell underwent a disintegration leaving the debris of the mitochondria and remnants of the vesicular component of the cytoplasm at the site of the hair cell in the fluid of Nuel's space. (Fig. 19).

A disorganization of the hair pattern was observed in later stages of degeneration and it was remarkable how well preserved the cuticular plate and the hairs might be in a cell with advanced disintegration in the lower parts of the cell. The IHCs were often even electron microscopically well preserved in areas where the OHCs had completely disappeared. Typical early signs of degeneration in these cells were the appearance of dark inclusion bodies and small vesicle granules in the subcuticular area, slight irregularities in the hair-bearing ends of some cells and nuclear pyknosis in some cells. (Fig. 20)

In some animals decapitated soon after the last injection, profound swellings below the IHCs were observed. These formations were identified as swollen afferent nerve endings and dendrites (Fig. 21) This finding has not been reported earlier after ototoxic drugs. That most of the swellings observed in our animals really are afferent nerve endings can be seen in the electron micrograph where a synaptic bar can be identified on the presynaptic side. Sometimes early degenerative changes were also observed in other nervous elements, such as the myelinated nerve fibers of the osseous spiral lamina and the spiral ganglion cells. The sequence of degeneration of the nerves has, however been analysed in a separate paper and will not be presented here.

The scanning electron microscope is a useful tool for illustration of the surface anatomy of the organ of Corti. Sometimes we observed a disarrangement of the sensory hairs of the IHCs at an early stage of degeneration. Since the stereocilia and the cuticular plate can be well preserved even in severe hair cell injury scanning electron microscopy is useful only in advanced stages of degeneration (Fig. 22)



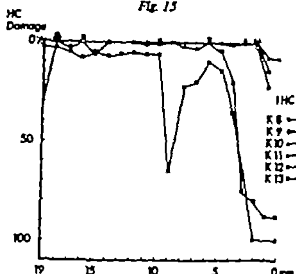
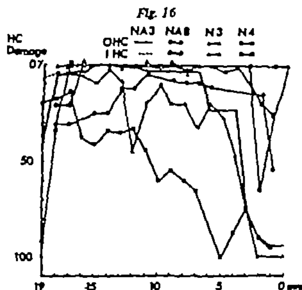


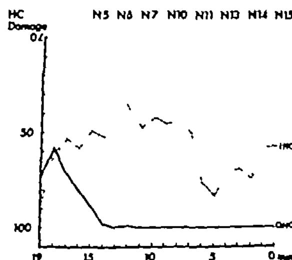
Fig. 14 Extent of OHC damage in 6 guinea-pigs given kanamycin 400 mg/kg for 6 or 7 days. The early stage of damage, when induced by kanamycin, affects the OHCs both in the hook and the upper basal coil, the first row of the OHCs is affected throughout the cohlea.

Fig. 15. Extent of IHC damage in the same animals as in Fig. 14 Degeneration was slight and regularly began in the basal part of the cochlea.

Fig. 16. Extent of hair cell damage in 4 guinea-pigs given neomycin 250 mg/kg for 7 or 8 days. The earliest signs of damage were regularly observed in the OHCs of the hook. In NA 8 some IHCs and the first row of the OHCs of the apex had also degenerated early

Fig. 17 Extent of the average combined IHC and OHC damage in 8 guinea-pigs given neomycin 250 mg/kg for from 5 to 8 days. Damage to the OHCs was uniformly severe whereas the damage suffered by IHCs varied considerably





1) No apparent damage light microscopically one animal, NA 2 This guinea-pig was administered neomycin for 7 days and decapitated on the 7th day The cytocochleogram revealed a normal hair cell population
2) Moderately severe damage, four animals NA 3 NA 8 N 3 and N 4 The damage was first seen in the basal coil, in the round window area as seen in Fig. 16 N 4 displayed a pattern of damage characteristic of neomycin with extensive loss of the IHCs in the apical 16–19 mm area with about 75 % preservation of OHCs in the same region.
3) Severe damage eight animals N 5 N 6 N 7 N 10 N 11 N 13 N 14 and N 15 As seen in Fig. 17 where the average

loss of the OHCs and of the IHCs are presented, these animals displayed severe degeneration of the OHCs. The IHCs were also severely injured in varying degrees. The peculiar capacity of neomycin to produce apical IHC damage was seen in most of these animals.

Electron microscopy

Electron microscopy (EM) often revealed early degenerative changes in the sensory cells while these still appeared normal under a light microscope. There were considerable differences in EM-findings between animals decapitated a few days after the last injection and animals which survived one month or more after cessation of treatment. Thus the latter group displayed fewer ultrastructural changes, and the degeneration detected by a light microscope coincided closely with EM findings. There were no noteworthy ultrastructural differences in animals treated with gentamicin, kanamycin or neomycin provided the pattern of degeneration was similar

In animals with severe OHC degeneration in the basal coil, early ultrastructural changes were usually seen in OHCs throughout the cochlea. The earliest changes included an increase in dark bodies unde the cuticular plate Some of these particles were spherical with variable electron density Others were lamellated and some of them were undoubtedly degenerated mitochondria, some were apparently lysosomes. In some cells a fibrous material appeared in the supranuclear part of the cell (Fig. 18)

The regular arrangement of fenestrated membranes along the sides of the cell was often disrupted in the early stage of degeneration. These membranes appeared disarranged in the cytoplasm and showed areas of condensation and rarefaction along the cell membrane. Such irregularities can normally be found in apical areas of the cochlea, but usually not in the lower turns.

A decrease in the ribosome content of the cell was a later finding often coinciding with a widening of interspaces between the layers of the fenestrated membranes along the sides of the OHCs. Vacuolization near the sides of the cells was noted and at the same time an increased number of vesicle granules appeared in the cytoplasm (and in some cells in the nucleus) Later the plasma membrane ruptured at several sites and the cell underwent a disintegration leaving the debris of the mitochondria and remnants of the vesicular component of the cytoplasm at the site of the hair cell in the fluid of Nuel's space. (Fig. 19)

A disorganization of the hair pattern was observed in later stages of degeneration and it was remarkable how well preserved the cuticular plate and the hairs might be in a cell with advanced disintegration in the lower parts of the cell. The IHCs were often even electron microscopically well preserved in areas where the OHCs had completely disappeared. Typical early signs of degeneration in these cells were the appearance of dark inclusion bodies and small vesicle granules in the subcuticular area, slight irregularities in the hair-bearing ends of some cells and nuclear pyknosis in some cells. (Fig. 20)

In some animals decapitated soon after the last injection, profound swellings below the IHCs were observed. These formations were identified as swollen afferent nerve endings and dendrites (Fig. 21) This finding has not been reported earlier after ototoxic drugs. That most of the swellings observed in our animals really are afferent nerve endings can be seen in the electron micrograph where a synaptic bar can be identified on the presynaptic side. Sometimes early degenerative changes were also observed in other nervous elements, such as the myelinated nerve fibers of the osseous spiral lamina and the spiral ganglion cells. The sequence of degeneration of the nerves has however been analysed in a separate paper and will not be presented here.

The scanning electron microscope is a useful tool for illustration of the surface anatomy of the organ of Corti. Sometimes we observed a disarrangement of the sensory hairs of the IHCs at an early stage of degeneration. Since the stereocilia and the cuticular plate can be well preserved even in severe hair cell injury scanning electron microscopy is useful only in advanced stages of degeneration (Fig. 22)

Fig. 18 Electron micrographs showing early signs of *OHC damage in guinea-pigs treated with A) gentamicin and B)* kanamycin. Cuticular plate and sensory hairs are intact. The number of dense bodies (DB) is increased in the subcuticular area. In B the amount of ribosomes is decreased. These micrographs show that the early degenerative changes induced by gentamicin and kanamycin were similar

St = stereocilia M = mitochondria FM = fenestrated membranes

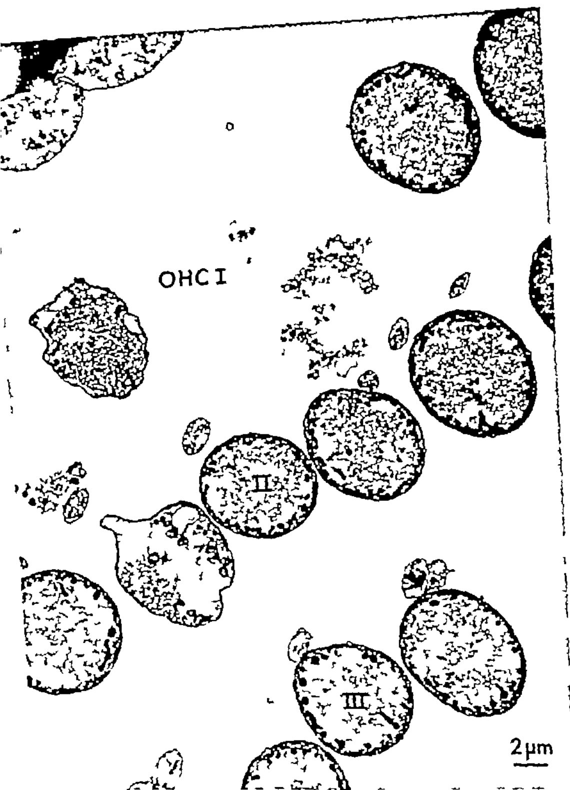


Fig. 12. Electron micrograph of surface section through the organ of Corti from a guinea-pig treated with kanamycin (K 8). OHC are at various stages of degeneration. One such cell in the second row displays mitochondrial damage, severe cytoplasmic degeneration and vacuolization of fenestrated membranes. Some cells in the first row have completely degenerated, with disruption of the plasma membrane leaving only debris. PC pillar cells

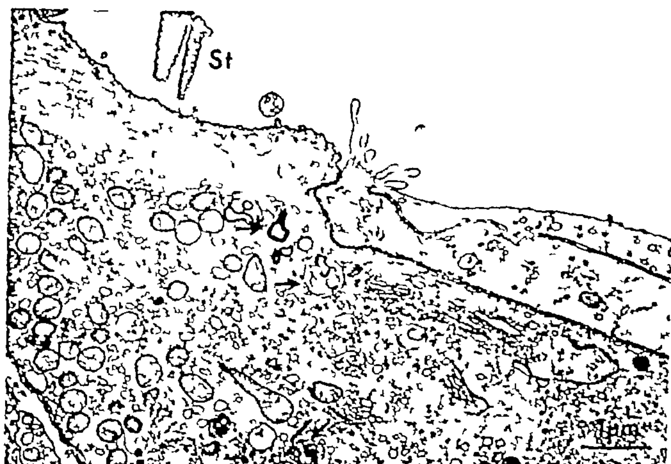


Fig. 20. Electron micrograph of an IHC of a guinea-pig showing early signs of gentamicin induced damage. Multiple lamellated bodies appear among the mitochondria, some of them formed by mitochondrial degeneration (arrows).



Fig. 21 Electron micrograph showing early degenerative changes in the neuronal elements in the cochlea of a guinea-pig treated with gentamicin. Some afferent nerve endings and dendrites below the IHC are swollen. NT = nerve terminal; D = dendrite

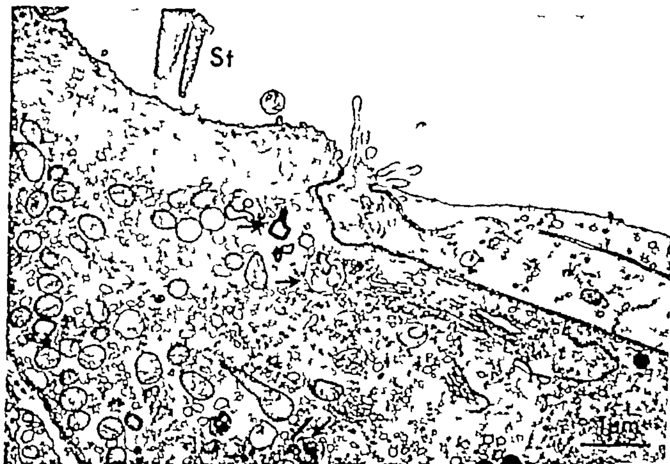


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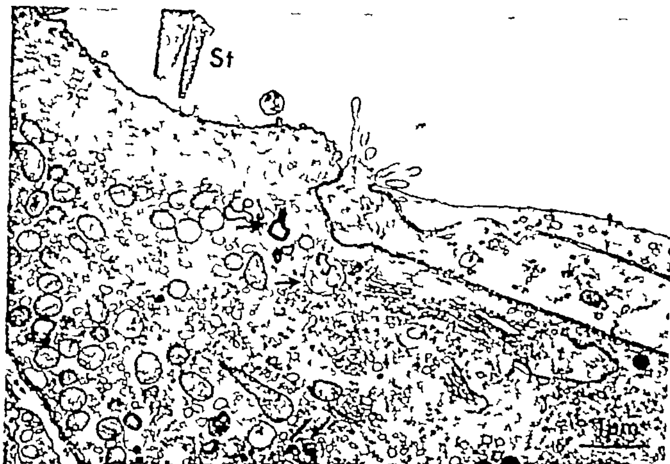


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ance in membrane permeability These changes were seen constantly immediately after exposure to noise but no longer on the following day (Spoendlin, 1971b) We were able to see the swellings of nerve endings in some cases a week or more after the last injection of the drug. Similar swellings have also been demonstrated by Wersäll et al. (1965) as early postmortem changes and can thus be difficult to distinguish from those caused by a delayed or defective fixation. For further discussion of the neuronal elements and their behaviour in the intoxicated animals, the reader is referred to a separately published paper (Ylikoski et al. 1974)

The degeneration pattern produced conforms fairly well with earlier reports indicating that the initial damage is in the basal coil, and the OHCs are the most susceptible to damage (Ruedi et al., 1953 Hawkins & Lurie 1953 Olivieri & Rossi, 1958 Hawkins, 1959 Ward & Fernandez, 1961 Beck & Krahl, 1962, Hawkins & Engström, 1964 Kohonen, 1965 Lundquist & Wersäll, 1967) The OHC loss almost constantly preceded the degeneration of the IHCs and the supporting structures. The pillar cells and the IHCs on the other hand, degenerated in a similar pattern in the basal part of the cochlea. In the upper coils the pillars were consistently well preserved even when hair cells had completely disappeared.

Although the general pattern of damage conformed well with earlier studies, there are some factors to which more attention should be paid because they are of great importance in the development and course of the damage. These factors are

1) the great individual variations in susceptibility to ototoxic drugs
2) differences in damage pattern after various antibiotics
3) the delayed effect of these basic aminoglycoside antibiotics, which makes the survival time important.

1) It was postulated by Hawkins (1967) that in experimental pathology studies ototoxic antibiotics can be used to produce experimental lesions and that it is possible to quantify the degree of injury in terms of dosage and length of treatment.

As has been shown in this paper however there are great variations in individual susceptibility to these antibiotics, thus general conclusions can be made only when a very large number of animals are used. These large individual differences are illustrated by examples in the following figures. In Fig. 12 and Fig. 13 diagrams of percentages of OHC loss and IHC loss are presented for four animals (K 1 K 3 K 6 and K 4) which all were given 300 mg/kg kanamycin for 11 or 12 days. Survival time was in all cases less than 4 days. The first two (K 1 and K 6) exhibit a moderate OHC damage in the basal part of the cochlea but the latter two (K 3 and K 4) have remaining OHCs only in the apical turn.

Fig. 23 demonstrates the average cochleogram for N 3 and for N 10. The dose of neomycin (250 mg/kg) and the duration of treatment (7 days) were equal for both of these animals and both of them survived more than 5 weeks after the last injection. However the former (N 3) experienced only moderate degeneration of cochlear sensory cells compared with the latter (N 10) which had only a few preserved hair cells left in the apical part of the cochlea.

Figs. 7 and 4 demonstrate hair cell pathology in animals G 23 and G 22. The former was treated with 100 mg/kg gentamicin for 16 days, the latter with the same dose for 21 days. As can be seen, the degeneration of sensory cells is severe in the cochlea of G 23 but only moderate in that of G 22

2) The differences in action of various ototoxic antibiotics yields somewhat different patterns of degeneration. As stated previously by Lindsay et al. (1960) in a human case, and by Kohonen (1965) in guinea-pigs, neomycin exhibits a great affinity for the IHCs of the apex. Kohonen postulated that the degeneration of the IHCs starts in the apex and progresses towards the base





Fig. 22. Scanning electron micrographs of the cochlea of A) a normal guinea-pig and B) a guinea-pig treated with neomycin. The sensory hairs and cuticular plate generally degenerate after the other parts of the cell have disintegrated. In B the cells of the first row of the OHCs have collapsed and the sensory hairs of the other two rows, as well as of the IHCs, are distorted.

DISCUSSION

It seems justified to assess the degree of damage to the organ of Corti by counting the missing and preserved hair cells since apparently the earliest degenerative changes after ototoxic antibiotics take place in the sensory cells (Wersäll 1959 Hawkins, 1959 Friedmann & Bird 1961 Wersäll & Hawkins 1962 Farkashidy et al. 1963 Duvall & Wersäll, 1964 Hawkins & Engström 1964 Lundquist & Wersäll, 1966, 1967)

Kellerhals et al (1967) found after intratympanic administration of kanamycin early toxic changes independent of hair cell degeneration in the first order neurone in the spiral ganglion Hawkins and Johnsson (1968) reported that kanamycin induced early degenerative changes in cells in the outer sulcus and the spiral limbus.

In our study the first degenerative changes were generally detected in the sensory cells especially in the first row of the OHCs in the basal coil. However in a few cases there was slight early damage in some neuronal elements, some spiral ganglion cells and some myelinated nerve fibres of the spiral lamina. In some animals afferent nerve endings and dendrites below the IHCs were swollen These findings confirm the suggestion of Kellerhals et al. (1967) that in addition to the secondary neural degeneration after ototoxic end organ injury a primary neural degeneration might appear which starts at the same time as changes in the neuroepithelium

The swellings of the nerve terminals below IHCs can be reversible and could thus be thought to serve as an explanation for the temporary threshold shifts after both ototoxic drugs and noise exposure Similar swellings were demonstrated by Beagley (1965) and Spoendlin (1971b) after acoustic trauma and by Spoendlin (1969b) after severe ischemia. Beagley interpreted these swellings as swollen supporting cells and Spoendlin identified them as swollen afferent dendrites, and he regarded these changes as the consequence of a disturb-

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and that this kind of damage pattern is seen in animals treated with neomycin and kanamycin In our results there is only 1 animal (K 3) treated with kana mycin which displays more extensive IHC damage in the apex than in the base of the cochlea. This kind of damage pattern was never found in animals treated with gentamicin, but one G 13 demonstrated a similar IHC degeneration both apically and basally On the other hand we had a great

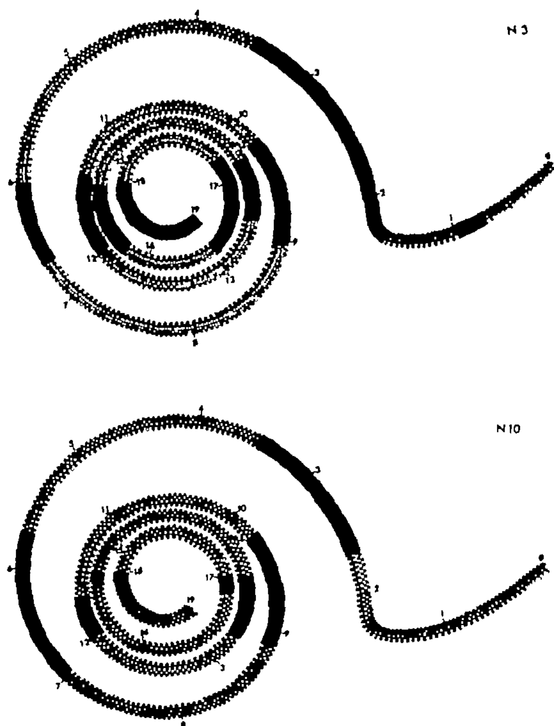


Fig. 23 Averaged cochleogram of 2 guinea-pigs treated with neomycin 250 mg/kg for 7 days. Both animals survived for longer than 5 weeks. Considerable variation in the extent of damage is apparent. Open circles normal cell groups. Filled circles damaged cell groups.

number of animals treated with kanamycin and gentamicin which experienced extensive IHC damage basally whereas the IHCs were nearly intact in the apex. After neomycin administration, however the degeneration of the IHCs in the apex was an almost constant finding. In some cases using neomycin it was possible to create a complete apical IHC loss when about 50 % of the OHCs were still present. In one animal (N 4) the cochlea was devoid of IHCs in the apical 2 mm area although 75 % of the OHCs were present there.

In the early stage of degeneration there was a scattered loss of the first row of OHCs relatively randomly distributed throughout the entire cochlea. This mild damage was independent of the antibiotic used. When the injury was somewhat greater and larger groups of adjacent OHCs were observed to be missing, the localisation of damage depended on the antibiotic. Neomycin seemed to destroy initially the OHCs of the extreme basal area, leaving other parts of the cochlea intact at the early stage Kanamycin and gentamicin, on the other hand, first destroyed the OHCs simultaneously in the hook area and in the upper basal coil while the area between was relatively well preserved. The OHCs of the hook were usually more severely affected and the degeneration was milder in the upper basal coil. When the damage progressed the OHCs in the basal coil all rapidly disappeared while the spiral spread of injury was slower towards the apex. There were also some differences in advanced stages of degeneration. Both kanamycin and neomycin destroyed the first row of OHCs much farther up than gentamicin. This is illustrated by a comparison of animals treated with gentamicin and kanamycin which displayed damage where the OHCs were missing in the lower half of the cochlea (Figs. 5 and 9) and the distance between the point where the third row of OHCs appeared and the point where the first row of OHCs appeared was in gentamicin animals averaged 3 mm in the kanamycin group 8 mm. This demonstrates that the damage pattern after gentamicin does not follow the distribution of the large, granulated nerve endings along the cochlea as has been earlier suggested in animals intoxicated with neomycin and kanamycin (Kohonen, 1965)

3) All the ototoxic aminoglycoside antibiotics accumulate in the fluids of the inner ear (Stupp et al. 1965 Voldrich, 1965 Stupp, 1970 Ylikoski et al. 1974) This capacity does, however vary somewhat depending on the antibiotic. From this it follows that these antibiotics exert their damaging action in different ways. Neomycin presumably has the strongest capacity to concentrate in the endolymph and perilymph because of its slow elimination rate (Ylikoski et al. 1974) and the degenerative changes produced by it can progress weeks or even months after the cessation of treatment (Leach, 1962) This makes the time elapsed from the start of treatment very important. This is illustrated in Fig. 24 where cochlear charts for NA 3 and N 14 are presented. Both of these animals were given neomycin 250 mg/kg. The duration of treatment was 8 days for NA 3 and it was sacrificed on the 8th day N 14 was treated for only 5 days and was decapitated 10 months later. Under a light microscope the organ of Corti of NA 3 appeared almost normal, except in the basal 3 mm area where the OHCs had suffered damage. It had almost totally disappeared in N 14 Although even electron microscopy revealed only the earliest signs of degeneration in the hair cells of NA 3 outside the damaged basal area, it is probable that if the animal had survived at least 1 month, it would have exhibited a pronounced damage of the hair cells as did the other animal treated with the same dose. Kanamycin and gentamicin had a milder delayed effect than neomycin but it is clear that if one

intends to quantify the degree of damage after ototoxic antibiotics in terms of dosage the survival time must be at least 3 or 4 weeks.

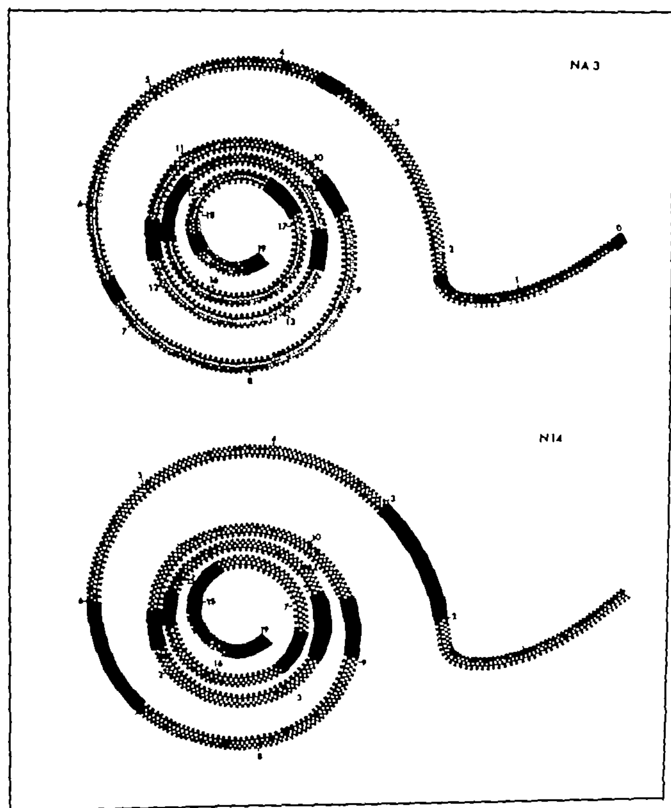


Fig. 24. Averaged cochleogram of 2 guinea-pigs treated with neomycin 250 mg/kg, NA 3 for 8 days and N 14 for 5 days. NA 3 survived 0 days, N 14 survived 10 months.

DEGENERATION OF NEURAL ELEMENTS IN THE COCHLEA OF THE GUINEA-PIG AFTER DAMAGE TO THE ORGAN OF CORTI BY OTOTOXIC ANTIBIOTICS

J Ylikoski, J Wersäll, B Björkroth

It was found as early as 1907 by Wittmaack that noise induced destruction of the organ of Corti and that this destruction was accompanied by neural degeneration in the osseous spiral lamina and in the spiral ganglion. Hoessli observed five years later that inner hair cells (IHCs) were more resistant to acoustic trauma than were outer hair cells (OHCs) and that the neural cells in the spiral ganglion degenerated first when IHCs were destroyed

In the earliest reports on the destruction of the organ of Corti induced by the administration of ototoxic antibiotics, such destruction was observed to be accompanied by the degeneration of corresponding neural elements (Ruedi et al., 1953 Riskaer et al., 1956 Olivieri & Rossi, 1958 Hawkins, 1959 Friedmann & Bird, 1961 Catalano et al., 1961) Several investigators, on the other hand have noticed no neural degeneration after the administration of such antibiotics apparently either because the degeneration they induced was limited to the OHCs and left the IHCs intact or the survival times of the experimental animals were too short for a full evaluation to be possible (Hawkins & Lurie 1953 Ward & Fernandez, 1961 Mesolella & Costa, 1960 Ardouin et al 1963 Farkashidy et al. 1963) In their investigation Farkashidy et al. were also able to see well-preserved outer spiral bundles (OSBs) and inner spiral bundles (ISBs) in specimens in which the OHCs had been destroyed. Engström et al. (1966) on the basis of the staining technique of Maillet concluded that the radiating fibres together with their nerve endings constituted a system especially sensitive to ototoxic antibiotics, whereas the long, spirally-running fibres of the ISB tunnel spiral b (TSB) and OSBs were less vulnerabl survived much longer

In his studies in the cat Schul (1953b) observed that in experim produced lesions the decrease in h population usually greatly exceede loss of spiral ganglion cells. The de ative changes in the spiral gangli peared to parallel more closely the of the injury suffered by the sup cells, particularly the pillar cells. findings have also been reported by (1965) and by Spoendlin (1966)

The intimate relationship between degeneration and the degeneration supporting cells was reported in r Hawkins & Johnsson (1968) by Jo & Hawkins (1972) and by Lawr Johnsson (1973) and in monkeys b bins et al. (1969)

On the other hand Kellerhals (1967) noted in guinea-pigs a clea lation between the degeneration c and ganglion cells. Similar finding reported by Bredberg (1968) who study on the human cochlea, observ a complete loss of sensory cells in segment was invariably accompanie complete loss of nerve fibres in sponding segment of the osseou lamina. Total or extensive loss of OH never associated with any noticeab faction of nerve fibres in the corresp sector of the osseous spiral lamin vided that the IHCs remained intact.

In a recent investigation in the pig, Spoendlin (1973) observed generation of nerve fibres after a lo the organ of Corti had been indu acoustic trauma and found that a









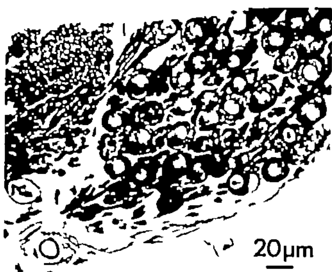




Fig. 1A

Aa. Radial section of a normal cochlea, including the organ of Corti.

Ab. Cross section of the spiral osseous lamina of a normal cochlea.

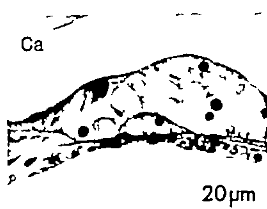
Ac. Radial section of the spiral ganglion of a normal cochlea.

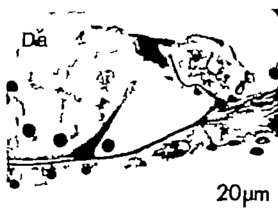
Fig. 1B

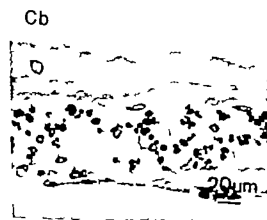
Ba. Section perpendicular to a region of the organ of Corti that was completely destroyed by neomycin (N 14/6 mm).

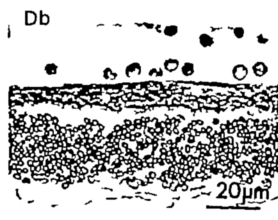
Bb. Cross section of the osseus spiral lamina from the same specimen as in Ba. About 20% of the myelinated fibres have survived.

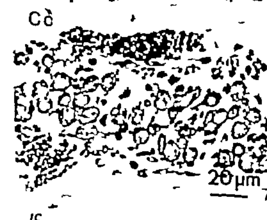
Bc. Radial section of the spiral ganglion from the same specimen as in Ba. About 1/3 of the spiral ganglion cells have survived.













1C

Section of the organ of Corti from specimen in which sensory cells are totally destroyed but in which the pillar cells were preserved (G 34/8 mm).
Cross section of the osseous spiral lamina from the same specimen as in Ca. About 15% of the myelinated nerve fibres have survived.
Radial section of the spiral ganglion from the same specimen as in Ca. From 1/3 to 2/3 of the spiral ganglion cells have survived.

Fig. 1D

Da. Section of the organ of Corti with intact inner but degenerated outer hair cells (G 21/9 mm).

Db. Cross section of the osseous spiral lamina from the same specimen as in Da. The number of myelinated nerve fibres appear normal.

Dc. Radial section of the spiral ganglion from the same specimen as in Da. The number of spiral ganglion cells appear normal.

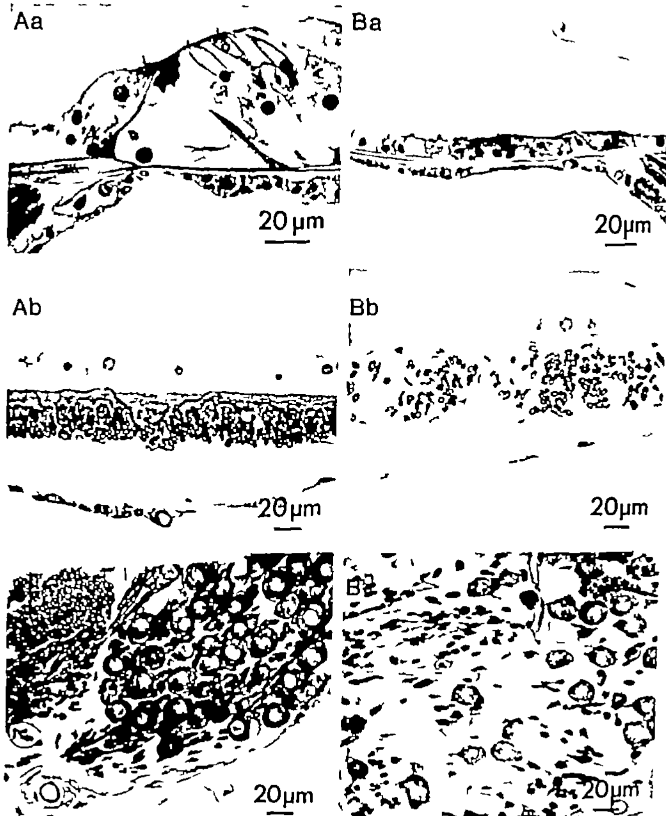


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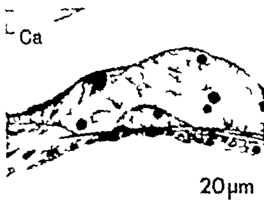
Ac. Radial section of the spiral ganglion of a normal cochlea.

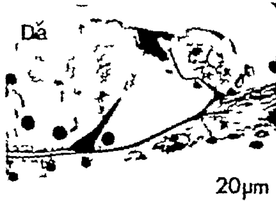
Fig. 1B

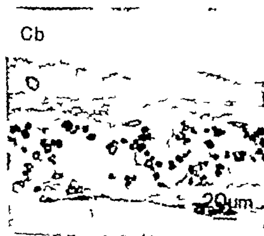
Ba. Section perpendicular to a region of the organ of Corti that was completely destroyed by neomycin (N 14/6 mm).

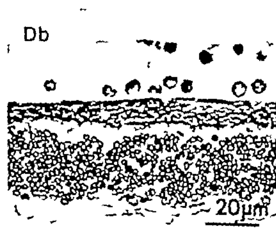
Bb. Cross section of the osseus spiral lamina from the same specimen as in Ba. About 20% of the myelinated fibres have survived.

Bc. Radial section of the spiral ganglion from the same specimen as in Ba. About 1/3 of the spiral ganglion cells have survived.









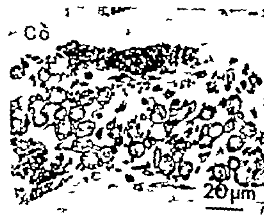




Fig. 1C

Ca. Section of the organ of Corti from specimen in which sensory cells are totally destroyed but in which the pillar cells were preserved (G 34/8 mm).

Cb. Cross section of the osseus spiral lamina from the same specimen as in Ca. About 15% of the myelinated nerve fibres have survived.

Cc. Radial section of the spiral ganglion from the same specimen as in Ca. From 1/3 to 2/3 of the spiral ganglion cells have survived.

Fig. 1D

Da. Section of the organ of Corti with intact inner but degenerated outer hair cells (G 21/9 mm).

Db. Cross section of the osseous spiral lamina from the same specimen as in Da. The number of myelinated nerve fibres appear normal.

Dc. Radial section of the spiral ganglion from the same specimen as in Da. The number of spiral ganglion cells appear normal.



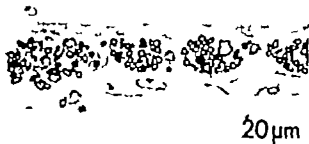


Fig. 1E

Ea. Section of the organ of Corti with intact outer but degenerated inner hair cells (N 4/18 mm).

Eb. Cross section of the osseous spiral lamina from the same specimen as in Ea. The number of myelinated nerve fibres appear normal.

ible to observe sensory cells to be completely destroyed while the pillar cells were almost intact

3) The OHCs were totally missing but the IHCs were well preserved In these instances the pillar cells and other supporting structures were invariably present and virtually intact
4) The OHCs were partially damaged with an average of 30 % missing. In such cases the IHCs and pillar cells were always intact except in the apex of neomycin-treated animals
5) The IHCs were completely destroyed in the apex while 50–75 % of the OHCs were preserved An example of this kind of degeneration was seen in animals treated with neomycin.

RESULTS

1) When the *organ of Corti* was *completely destroyed* (Fig 1B) the spiral ganglion still contained some ganglion cells. The number of neurons in the intraganglionic spiral bundle was clearly reduced and in the osseous spiral lamina only a few myelinated and unmyelinated nerve fibres remained The quantitative estimate of the remaining nervous elements provided the results shown in Table 1 The number of surviving spiral ganglion cells was unexpectedly high more than 1/3 of the *normal number in three out of four* specimens studied In only one specimen was their number less than 1/3 of normal

CASE	DURATION OF TREATMENT	SURVIVAL TIME	IGSB	SPIRAL GANGLION CELLS	OSSEOUS SPIRAL LAMINA
N14/5 mm	5 days	10 months	1/3-2/3	1/3-2/3	418 fibers/mm
N14/9 mm	5 - -	10 - -	1/3-2/3	1/3-2/3	214 - -
K14/5 mm	20 - -	2 - -	> 2/3	< 1/3	520 - -
N13/6 mm	7 - -	3 5 - -	> 2/3	1/3 2/3	253 - -

Table 1 *Quantitative analysis of remaining neurons in those specimens in which the organ of Corti was completely destroyed. IGSB = intraganglionic spiral bundle*

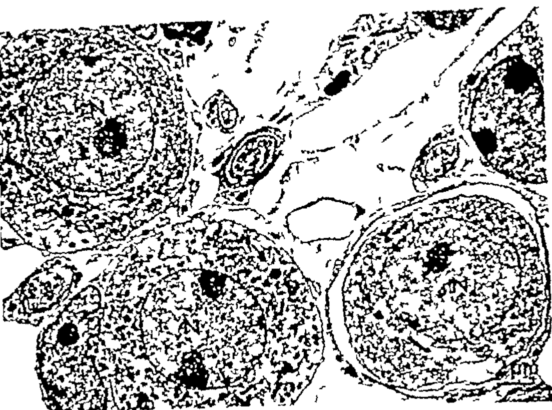


Fig. 2. Low magnification electron micrograph of th spiral ganglion from specimen in which th organ of Corti was completely destroyed by neomycin (N 14/5 mm). The cells are well preserved, displaying only slight abnormalities such as an increase in the number and size of multivesicular bodies and pigment granules (arrows), and vesiculation of the nucleoli (N). Two of these cells are unmyelinated.

The intraganglionic spiral bundle was well preserved in two specimens in which more than 2/3 of the fibres were still present. In two other specimens the rarefaction was somewhat greater with between 1/3 and 2/3 of the neurons surviving. The number of myelinated nerve fibres in the osseous spiral lamina was extensively reduced in all specimens examined. The number of remaining fibres varied between 214 and 520 per millimetre. The myelinated fibres were usually easy to follow from the spiral ganglion to the habenula perforata but not beyond and no identifiable nerve fibres were detected within the remnants of the totally collapsed organ of Corti.

Althought the surviving nerve fibres were usually ultrastructurally normal, electron microscopy sometimes revealed degenerative changes that were not observable by light microscopy. The surviving spiral ganglion cells of animals belonging to this group appeared even finestructurally almost normal. Slight abnormalitres consisted of an increase in the number and size of multivesicular bodies and pigment granules in the perikaryon. Some cells also displayed an increase in the prominence and distention of the Golgi vacuoles, a swelling of the mitochondria and an expansion of the cisternae of the granular endoplasmic reticulum. The nuclei of such cells contained nucleoli that often had a vesiculated appearance and a large amount of nucleolus-enriched chromatin. (Fig. 2)

The relative number of unmyelinated filamentous type II ganglion cells was high in animal N 14 in which about





Fig. 1E

Ea. Section of the organ of Corti with intact outer but degenerated inner hair cells (N 4/18 mm).

Eb. Cross section of the osseous spiral lamina from the same specimen as in Ea. The number of myelinated nerve fibres appear normal.

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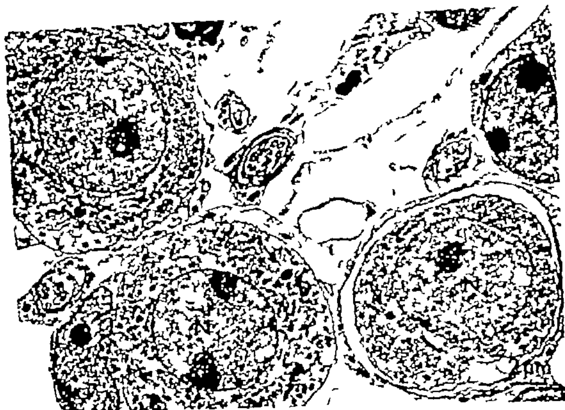


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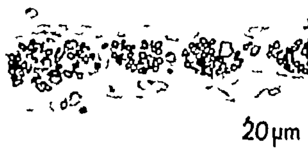


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Fig 3. Low magnification electron micrograph of the spiral ganglion from a specimen in which all the sensory cells had degenerated but in which the pillar cells had survived (K 14/9 mm). Signs of degeneration in these spiral ganglion cells are the distention of Golgi vacuoles, the expansion of the cisternae of the granular endoplasmic reticulum (arrows), and the movement of Nissl substance nearer the nucleus.

the last injection were relatively short. In one, K 4 that was decapitated on the 16th day after the beginning of treatment, light microscopic countings of the nerve fibres in the ganglion and osseous spiral lamina were the same as in normal animals. The other, K 15 was decapitated on the 47th day after the start of treatment. In the quantitat ive analysis of this specimen there was only a moderate reduction in the number of nerve fibres in the spiral ganglion and lamina. Because these two specimens varied even ultrastructurally from the rest of this group they are mentioned separately

Electron microscopy revealed a picture of the cells in the spiral ganglion and spiral lamina that resembled that of the foregoing group In some spiral ganglion cells the mitochondria were swollen and their cristae were disarranged. In addition the number and size of multivesicular bodies, dark bodies and Golgi vacuoles had increased. Some cells displayed large vacuoles and their Nissl substance had moved nearer the nucleus leaving the cytoplasm adjacent to the cell membrane vacant and thus less electron dense. (Fig. 3) Occasional cells exhibited extensive degeneration with severe vacuolization in karyoplasm that had shrunk. The majority of the surviving ganglion cells had a thin myelin sheath and resembled the regular type I ganglion cells. Approximately 25 % of the ganglion cells were unmyelinated.

About 30 % of the surviving axons of the intraganglionic spiral bundle and the osseous spiral lamina showed ultrastructural degenerative changes similar

CASE	DURATION OF TREATMENT	SURVIVAL TIME	IGSB	SPIRAL GANGLION CELLS	OSSEOUS SPIRAL LAMINA	TUNNEL CROSSING FIBERS tot	upp	bas	ISB	TSB	OSB 1	2	3	tot
K14/6 **	20 days	64 days	> 2/3	< 1/3	520	0	0	0	0	0	0	0	0	0
K14/9 **	20 -	64	1/3–2/3	< 1/3	535	0	0	0	0	0	0	0	0	0
634/8 **	14 -	98	> 2/3	1/3–2/3	403	61	50	11	72	14	17	9	6	32
634/11**	14	98	1/3 2/3	1/3–2/3	174	48	35	13	45	8	29	15	11	55
K 4/9 **	12 -	4	> 2/3	> 2/3	2193	211	186	25						
K15/5 **	20 -	27	> 2/3	> 2/3	1875	307	288	19	57	19	19	13	10	42

Table 2. *Quantitative analysis of remaining neurons in those specimens in which all the sensory cells were destroyed but in which the supporting cells and the tunnel of Corti survived. ISB = inner spiral bundle, TSB = tunnel spiral bundle, OSB = outer spiral bundle.*

50 % of the surviving ganglion cells were unmyelinated in both the sections studied In two other animals all the preserved ganglion cells had a myelin sheath. The sheath was normally thin but these myelinated ganglion cells were otherwise similar to the regular type I ganglion cells. The subtle abnormalities observed in this group of animals randomly affected both myelinated and unmyelinated ganglion cells.

More than 50 % of the surviving nerve fibres in the intraganglionic spiral bundle appeared to be ultrastructurally normal The rest of the axons exhibited some greater or lesser degenerative change, most often a deformation of the myelin sheath. The fibres had then often lost their typical roundoval con figuration and had been transformed into collapsed figures that consisted only of a narrow core containing a greatly reduced amount of axoplasm The lamellated construction of the myelin sheath was, however generally well preserved. The axoplasm of many nerve fibres displayed diminished electron density and the number of neurofilaments and microtubules was often reduced Sometimes the axoplasm had become dark and held dark inclusion bodies and vacuoles that appeared to be enlarged agranular endoplasmic reticulum Unmyelinated nerve fibres seemed to be less affected by such degenerative changes than myelinated fibres.

The myelinated axons in the osseous spiral lamina exhibited ultarastructural changes similar in character and frequency to those seen in the intraganglionic spiral bundle. A characteristic abnormality was the collapse of the otherwise normal myelin sheath as a result of the diminution of axoplasm

2) When the *tunnel of Corti was preserved* (Fig. 1C) although often tilted, and *all the hair cells had disappeared,* neural damage in the spiral ganglion and in the osseous spiral lamina was similar to that observed when the organ of Corti had been completely destroyed (Table 2) Approximately 1/3 of the spiral ganglion cells remained. The number of myelinated neurons in the intraganglionic spiral bundle was reduced to about 1/3 to 2/3 of the normal number The osseous spiral lamina contained between 174 and 535 myelinated fibres per millimetre In these specimens it was clearly seen that when occasional IHCs had survived the density of nerve fibres in the osseous spiral lamina was also greater in that area.

This group contained specimens from two animals whose survival times after



Fig 3. Low magnification electron micrograph of the spiral ganglion from a specimen in which all the sensory cells had degenerated but in which the pillar cells had survived (K 14/9 mm). Signs of degeneration in these spiral ganglion cells are the distention of Golgi vacuoles, the expansion of the cisternae of the granular endoplasmic reticulum (arrows) and the movement of Nissl substance nearer the nucleus.

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Electron microscopy revealed a picture of the cells in the spiral ganglion and spiral lamina that resembled that of the foregoing group. In some spiral ganglion cells the mitochondria were swollen and their cristae were disarranged. In addition the number and size of multivesicular bodies, dark bodies and Golgi vacuoles had increased. Some cells displayed large vacuoles and their Nissl substance had moved nearer the nucleus leaving the cytoplasm adjacent to the cell membrane vacant and thus less electron dense. (Fig. 3) Occasional cells exhibited extensive degeneration with severe vacuolization in karyoplasm that had shrunk. The majority of the surviving ganglion cells had a thin myelin sheath and resembled the regular type 1 ganglion cells. Approximately 25 % of the ganglion cells were unmyelinated.

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Fig. 4. Low magnification electron micrograph of the osseous spiral lamina *from* a specimen in which all the sensory cells were destroyed but in which the supporting cells had survived (G 34/11 mm) Only about 10% of the myelinated nerve fibres in this section remained and *some of these exhibited* degenerative changes such as a collapsed myelin sheath and a reduced amount of axoplasm (arrow).

to those described in the fibres of the foregoing group (Fig. 4)

Some unmyelinated dendrites within *the organ of Corti were still present in* two sections (G 34) but the number of tunnel-crossing fibres had been reduced to 1/10 of normal The spirally running fibres in these sections were somewhat better preserved although also clearly diminished in number The outer spiral fibres moreover appeared better preserved than either the tunnel or the inner spiral fibres.

Sections from two animals with relatively short survival times revealed more neurons than other specimens in this group They appeared to be undergoing degeneration and abnormalities, manifested as degenerative changes in the karyoplasm similar to those mentioned in the first group were frequently observed (Fig. 5) In addition the myelin sheath was often disarranged and vacuolized at a stage when the axoplasm still contained a relatively intact complement of neurofilaments and microtubuli In the organ of Corti both radial and spiral dendrites were observed to have undergone degeneration The neurilemma was often swollen and enclosed axoplasm that lacked neurofilaments sometimes the neurilemma had ruptured releasing its contents into the fluid space.

3) In many cochleas *the outer hair cells* were completely *destroyed* (Fig 1D) in the lower half of the cochlea while the set of *inner hair cells* was still *essentially intact.* In such specimens light microscopy revealed a normal density of nerve fibres in the osseous spiral lamina and in the spiral ganglion as well as the normal number of neural elements in these locations (Table 3)

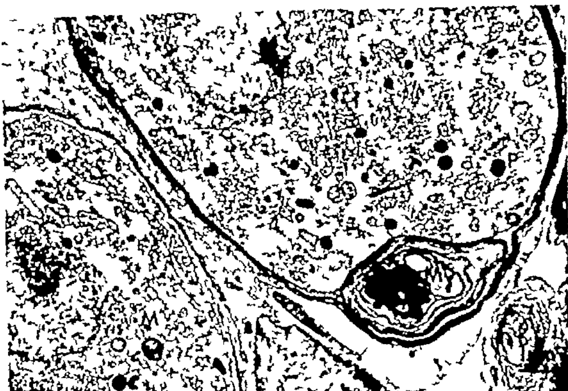
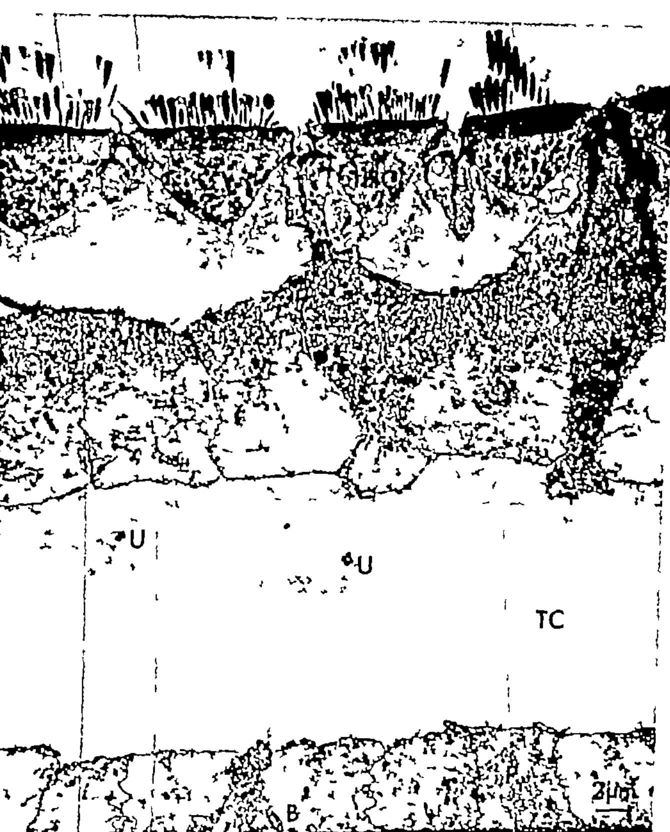


Fig. 3 Electron micrograph of the spiral ganglion from specimen in which all the sensory cells were destroyed by kanamycin (K 4/9 mm). Because survival time had been short (4 days), the number of neurons was still nearly normal, but many of them displayed early degenerative changes such as an increase in the number and prominence of pigment granules (P) and multivesicular bodies (M), and the formation of myelin figures (My) at the cell poles.

The spiral ganglion cells in these specimens generally appeared normal even by electron microscopy. Some cells displayed degenerative changes such as vacuolization of the cytoplasm with an increase in the prominence and number

CASE	DURATION OF TREATMENT	SURVIVAL TIME	IGSB	SPIRAL GANGLION CELLS	OSSEOUS SPIRAL LAMINA	TUNNEL FIBERS tot	upp	bas	ISB	TSB	OSB 1	2	3	tot
K 5/3 **	8 days	70 days	2/3	2/3	2348	282	230	52						
K 6/6 **	8	70			2310	415	273	142	71	37	20	19	18	57
K 6/9 **	8	70			2400	489	352	137	180	70	31	23	19	73
621/5 5	21	43			2290				135	127	29	23	28	80
621/9 **	21	43			2023	639	528	111	210	107	42	30	23	95
624/6 *	18	32			2180	671	627	44	160	130	34	21	25	80
624/9 **	18	32			2392	739	655	84	160	100	33	11	16	60
K12/8 **		128			2281	252	228	28	181	80	25	18	29	70

Table 3 *Quantitative analysis of remaining neurons in those specimens in which all the outer hair cells were destroyed but in which the inner hair cells and the supporting cells were virtually intact.*



ig. 6. Electron micrograph of a longitudinal section of e organ of Corti from a specimen in which all the outer air cells had degenerated but in which the inner hair cells HC) were intact. In such specimens, the unmyelinated tunnel-crossing fibres, both upper (U) and basilar (B), were intact provided the pillar cells had survived. TC tunnel of Corti, P = pillar cell.

of Golgi zones, the formation of whirls of myelin lamellae in the cellular poles and finally disruption and fragmentation of the myelin sheaths.

The myelinated and unmyelinated nerve fibres within the intraganglionic spi-



Fig. 7 High magnification electron micrograph of the tunnel of Corti from a specimen in which [illegible] was similar to that as seen in Fig. 6. The number and state of both upper (U) and basilar (B) tunnel-crossing fibres appear normal. BM, basilar membrane; P, pillar cell.

ral bundle and spiral lamina usually appeared to be finestructurally normal. In occasional specimens the axoplasm had become increasingly vacuolated and darkened and myelin figures had formed

The number and state of the unmyelinated dendrites in the organ of Corti in this group of specimens varied somewhat. In one section (N 13/9 mm) only a few fibres were present in the tunnel of Corti and the feet of the outer pillars were severely swollen. The spiral bundles were better preserved although slightly diminished in number In another neomycin-treated animal (N 6) the number of both the upper efferent fibres and the basilar fibres appeared reduced in three separate sections (5 6 and 9 mm) The spiral fibres were also reduced in number in the most basal section of this cochlea. In two genta-

micin-treated animals (G 21 and G 24) the spiral bundles appeared normal except in one section of the former animal (G 21/5,5 mm) in which the number of fibres in the ISB was clearly diminished Tunnel-crossing fibres appeared well preserved In G 24 there was an unusually high number of efferent tunnel-crossing fibres in both sections studied (Fig 6 and Fig. 7) In both neomycin-treated animals in this group the surviving fibres in the tunnel frequently displayed signs of degeneration These axons were swollen their neurofilaments and microtubules were strikingly rarefied and destroyed and their mitochondria were sometimes distended.

4) *A partial loss of outer hair cells* alone was never associated with either rarefaction or loss of radial spiral nerve fibres in the corresponding sector of the spiral ganglion or osseous spiral lamina (Table 4) The unmyelinated dendrites within the organ of Corti also remained unaltered both in number and appearance In one specimen (G 21/13 mm) swollen afferent nerve endings were observed below the IHCs, a region that appeared normal in two sections from the lower parts of the same cochlea (9 mm and 5,5 mm) That some such swellings were in fact afferent nerve endings is evident from the Fig. 8 in which the synaptic bar is identifiable on the presynaptic side

5) *A complete loss of inner hair cells* in a region of the organ of Corti where *outer hair cells* had only *partially disappeared* (Fig. 1E) was usually observed in the apical part of the cochlea of the animals treated with neomycin. These regions displayed an unexpectedly well preserved pattern of nerve fibres in the osseous spiral lamina In fact, in two specimens the number of myelinated laminar fibres was essentially normal (Table 5) The spiral ganglion was not studied at this level. The unmyelinated dendrites in the organ of Corti,

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G21/13 mm	21 days	43 days	>2/3	>2/3	416	322	94	158	95	52	18	18	88
G15/13 mm	29 - -	24 -	>2/3	>2/3	-	-	-	150	85	51	19	21	91
Norm/13 mm	- -		>2/3	>2/3			-	145	84	50	20	19	89

Table 4 *Quantitative analysis of remaining neurons in those specimens in which only some of the outer hair cells had degenerated as compared with the number of neurons in the corresponding region of a normal guinea-pig*

CASE	DURATION OF TREATMENT	SURVIVAL TIME	OSSEOUS SPIRAL LAMINA FIBERS/mm	TUNNEL CROSSING FIBERS total	ISB	TSB	OSB 1	2	3	tot
N4/18 mm	7 days	39 days	1148	171	70	24	33	32	18	83
N8/18 mm	8	70	1176	145	85	23				
Norm/18 mm			1100	186	75	42	32	16	20	78

Table 5 *Quantitative analysis of remaining neurons in those specimens in which all the inner hair cells had degenerated but only a portion of the outer hair cells were damaged (more than 50% remaining) as compared with the number of neurons in the corresponding region of a normal cochlea*



Fig 4 Electron micrograph showing the neurons below an inner hair cell in specimen in which the sensory cells are virtually intact. Swelling of some neural elements are apparent. IP = inner pillar, ISB = inner spiral bundle, D = dendrite, E = nerve ending. Arrow = synaptic bar.

both spiral and radial, appeared quantitatively as well as qualitatively normal. A spatial differentiation between upper tunnel-crossing fibres and basilar fibres was not possible at this 18 mm level.

DISCUSSION

1) *Effect of ototoxic aminoglycoside antibiotics on the cochlea*

Abundant data exist about the effect of ototoxic antibiotics on the sensory cells and neurons of the cochlea. Evidence points to a distinct spatial pattern of degeneration among the hair cells. Neural elements had been stated to degenerate almost simultaneously with hair cells in a distinct sequential pattern that parallel that of the hair cells but that lags slightly behind (Kohonen, 1965). Electron microscopic studies have shown that neural elements are still intact when obvious

micin-treated animals (G 21 and G 24) the spiral bundles appeared *normal* except in one section of the former animal (G 21/5 5 *mm*) *in which the* number of fibres in the ISB was clearly *diminished* *Tunnel-crossing* *fibres* appeared well preserved In G 24 there was an unusually high number of efferent tunnel-crossing fibres in both sections studied (Fig 6 and Fig 7) In both neomycin-treated animals in this group the surviving fibres in the tunnel frequently displayed signs of degeneration. These axons were swollen their *neurofilaments and microtubules* were strikingly rarefied and destroyed and their mitochondria were sometimes distended

4) *A partial loss of outer hair cells* alone was never associated with either rarefaction *or loss of radial spiral nerve* fibres in the corresponding sector of the spiral ganglion or osseous spiral lamina (Table 4) The unmyelinated dendrites within the organ of Corti also remained unaltered both in number *and appearance. In one specimen* (G 21/13 mm) swollen afferent nerve endings were observed below the IHCs, a region that appeared normal in two sections from the lower parts of the same cochlea (9 mm and 5,5 mm) That some such swellings were, in fact afferent nerve endings is evident from the Fig. 8 in which the synaptic bar is identifiable on the presynaptic side.

5) A *complete loss of inner hair cells* in a region *of the organ of Corti where outer hair cells* had only *partially disappeared (Fig. 1E) was usually* observed in the apical part of the cochlea *of the animals treated with neomycin.* These regions displayed an unexpectedly well preserved pattern of nerve fibres in the osseous spiral lamina. In fact, in two specimens the number of myelinated laminar fibres was essentially normal (Table 5) The spiral ganglion was not studied at this level The unmyelinated dendrites in the organ of Corti,

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G15/13 mm	29 -	24 -	>2/3	>2/3	-	-	-	150	85	51	19	21	91
Norm/13 mm	- -	- -	>2/3	>2/3	-	-	-	145	84	50	20	19	89

Table 4 *Quantitative analysis of remaining neurons in those specimens in which only some of the outer hair cells had degenerated as compared with the number of neurons in the corresponding region of a normal guinea-pig*

CASE	DURATION OF TREATMENT	SURVIVAL TIME	OSSEOUS SPIRAL LAMINA FIBERS/mm	TUNNEL CROSSING FIBERS total	ISB	TSB	OSB 1	2	3	tot
N4/18 mm	7 days	39 days	1148	171	70	24	33	32	18	83
N6/18 mm	8	70	1176	145	83	23				
Norm/18 mm			1100	186	75	42	32	16	20	78

Table 5 *Quantitative analysis of remaining neurons in those specimens in which all the inner hair cells had degenerated but only a portion of the outer hair cells were damaged (more than 50% remaining) as compared with the number of neurons in the corresponding region of a normal cochlea.*

degeneration after the end organ has been damaged.

To distinguish between the efferent and afferent fibres that cross the tunnel is extremely difficult in the guinea-pig. Although the efferent fibres to the OHCs usually cross the tunnel of Corti at a higher level than their afferent counterparts, there is often an intermingling of efferents that run at a relatively low level and afferents that sometimes freely cross the tunnel in the Cortilymph. The distinction we employed in our analysis is, however based on a spatial separation.

The tunnel-crossing fibres were usually well preserved as long as the IHCs and supporting cells were essentially intact. In one section, however these fibres had degenerated severely even though the IHCs were nearly intact and the OHCs were missing but when the feet of the outer pillar cells were markedly swollen. It seems likely therefore that for tunnel-crossing fibres to survive the intact state of supporting cells is important. When these fibres degenerated, moreover both efferent and afferent fibres were randomly affected.

In examining the apical region of the cochlea (18 mm) we made a surprising observation. In spite of the complete loss of IHCs and about a 50 % loss of OHCs, the myelinated fibres in the osseous spiral lamina and the unmyelinated fibres in the organ of Corti were as numerous as in normal control animal. In this region all the tunnel-crossing fibres appeared to be afferent.

3) *Ultrastructural signs of degeneration in the osseous spiral lamina and spiral ganglion*

Only a few electron microscopic studies of the degenerative changes that take place in the spiral ganglion cells after administration of ototoxic antibiotics have been carried out.

Awataguchi et al. (1967) observed, in kanamycin-treated guinea-pigs, degenerative changes that consisted of a dilatation of the endoplasmic reticulum a widening of Golgi vacuoles, swelling of mitochondria whose cristae had become deformed, a decrease in the electron density of the cytoplasmic matrix, swellings of the nuclear membrane and finally vesiculation of the myelin sheath. Unmyelinated ganglion cells were more susceptible to such degenerative changes than were myelinated cells

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The signs of mild injury that we observed consisted of an increase in the number and size of multivesicular and pigment bodies, a distention of Golgi vacuoles, swelling of mitochondria and an expansion of the cisternae of granular endoplasmic reticulum. The myelin sheath was usually still intact in animals that had survived several months. In more acutely affected animals however it was often deformed, sometimes even disrupted or vacuolized, and in some such severly affected cells whirls of myelin lamellae had accumulated at the poles. Spiral ganglion cells that lacked a myelin sheath were often better preserved than cells encased in myelin.

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In our investigation the earliest degenerative changes *usually appeared in the* hair cells The spiral ganglion and osseous spiral lamina were invariably normal *by light microscopy when the OHCs* had been partially or completely destroyed and the IHCs were still essentially intact In a few animals, however electron microscopy revealed early signs of *neural degeneration while the* correspond ing hair cells still appeared nearly normal These changes were seen as swellings below *the IHCs, apparently swollen afferent nerve* endings and dendrites. Such swellings were observed in one animal 11 days after the beginning *of treatment and in another as* long as 43 days after the cessation of treatment. *Similar* degenerative changes have been reported after ischemia (Spoendlin 1969b) and after acoustic trauma (Beagley 1965 Spoendlin 1971b) Whether such changes are to be interpreted as true *pathological findings or as fixation artefacts* remains to be determined.

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We observed some degenerative changes in the radial neurons within the organ of Corti, in the osseous spiral lamina and in the spiral ganglion cells in one animal (K 4) sacrificed 16 days after the beginning of treatment. In another animal (K 15) one that survived 4 weeks, the number of nervous elements was reduced at all of these three levels but the degeneration was not as obviously complete as it was in K 14 an animal that had survived for 64 days. It would appear therefore that it takes no less than one month for the degeneration of nerve fibres in the osseous spiral lamina and in the spiral ganglion to run its course.

lation and occasional darkening of the axoplasm, the appearance of various inclusion bodies in the axoplasm and the formation of myelin figures. At later stages the myelin sheath had often collapsed and the axoplasm which was sometimes both less electron dense than normally and devoid of neurofilaments and tubuli had markedly diminished in quantity

4) The nature of surviving nervous elements

A) Surviving fibres in the osseous spiral lamina

Myelinated laminar fibres consist of afferent neurons of both OHCs and IHCs. According to Spoendlin (1969a) the nerve fibres that supply the IHCs in the cat are far more numerous than those that innervate the OHCs, the ratio being 95:5 It could therefore be expected that after the destruction of all OHCs the number of myelinated fibres would be reduced by 5 % Morrison et al. (1974) estimated the percentage of afferent fibres associated with OHCs to consist of approximately 10–15 % of all myelinated laminar fibres in the guinea-pig. Unfortunately estimates of variations in the number of fibres made with the present technique does not allow for any conclusion related to a variation below about 20 %.

In several cochleas in which the organ of Corti was severely damaged between 10 and 25 % of the fibres in the lamina survived It has been pointed out that a portion of the myelinated laminar fibres belong to the efferent olivocochlear system (Terayama, 1969 1971 Morrison et al 1974) Morrison et al have also shown that these efferent fibres comprise about 25–30 % of all laminar fibres in the guinea-pig. The question of whether the fibres that survived in our study are afferents to type II unmyelinated ganglion cells (Spoendlin 1973) or efferents that have undergone partial degeneration (as did the fibres in the intraganglionic spiral bundle in most specimens) remains to be answered.

B) Surviving spiral ganglion cells

More than 50 % of the preserved spiral ganglion cells in cochleas in which all sensory cells had been destroyed were myelinated. These spiral ganglion cells regularly displayed a relatively thin myelin sheath and could thus be considered to be type III ganglion cells as classified by Spoendlin (1973) although they were in no other way morphologically different from the regular type I ganglion cells. The karyoplasm and nuclei of unmyelinated ganglion cells were usually not appreciably different from that of type I ganglion cells. Their abundance, however raises the question of whether they were true primary unmyelinated cells or cells that had lost their myelin sheath as the result of degeneration.

Rate of neural degeneration

Wallerian or descending degeneration occurring when the axon is interrupted at any point is known to take place quickly and to lead to a complete breakdown of the distal portion of the axon. After transection of the olivocochlear bundle rapid changes of this kind were observed by Iurato (1961) in rats after 16 hours, by Kimura & Wersäll (1962) in the guinea-pig and by Smith & Rasmussen (1963) in the chinchilla after 2–3 days. Spoendlin saw obvious degeneration in the efferent nerve endings in the cat one week after transection and changes had developed fully after 3 weeks.

Retrograde degeneration, another type of degeneration that occurs when the axon is interrupted or the end organ is destroyed affects the proximal portion of the axon Such degeneration is known to occur slowly and is usually incomplete.

We know that degeneration of sensory cells can take place within a few days after the application or introduction of a damaging agent, only scant data exists, however about the rate of neural degeneration when the primary lesion affects the organ of Corti. Lurie et al. (1944) noticed the first degenerative changes in the laminar nerve fibres of the guinea-pig 9 days after exposure to noise whereas degeneration of the ganglion cells did not take place until 3–4 weeks after such exposure.

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CORRELATION BETWEEN PURE TONE AUDIOGRAM AND COCHLEAR PATHOLOGY IN GUINEA PIGS INTOXICATED WITH OTOTOXIC ANTIBIOTICS

J Ylikoski

According to current knowledge, sound energy is converted into action potentials in the auditory nerve in the organ of Corti This process of transduction is generally considered to be carried out by the hair cells. In spite of the accumulation of more and more experimental and clinical data regarding the structural arrangement and the physiology of the organ of Corti there still exists a gap in the knowledge concerning the role of different types of hair cells in the transduction mechanism

Another generally accepted concept is that the cochlea functions not only as a transducer but also as a frequency and temporal analyzer According to the place principle points of maximal stimulation for each frequency are spatially arranged along the basilar membrane so that the area of optimal excitation for high frequencies is situated near the round window for the low frequencies the corresponding site is near the helicotrema. If we accept that the place principle is functioning, at least at higher frequencies, and that the hair cells are responsible for the auditory transduction then it would seem possible to study the specific role of different kinds of hair cells as well as the frequency localisation along the basilar membrane of the cochlea. This can be done by causing damage to a selected part of the cochlear partition and assessing the residual functional capacity of the cochlea by audiometric methods combined with microscopic examination of the organ of Corti.

A useful way of producing desired and selective damage inside the cochlea without causing mechanical injury or an intermixing of the cochlear fluids is to administer ototoxic antibiotics whose effect can be quantified in terms of dosage and length of treatment. The ototoxic potentials of the, useful but unruly family of basic streptomyces antibiotics" (Hawkins, 1959) was realized soon after their introduction and some of them were shown to possess a special cochleotoxic property

Although there is abundant data regarding the damage pattern in the cochlea after treatment with aminoglycoside antibiotics correlated to suprathreshold hearing measurements (pinnareflex in guinea-pigs, cochlear microphonics) there are still very few direct correlative studies between audiometric hearing threshold measurements and cochlear pathology The only studies of this kind published so far were carried out by McGee and Olzewski (1962) in four trained cats which had been treated with streptomycin and dihydrostreptomycin by McGee et al (1969) who studied one trained cat treated with gentamicin by Stebbins et al. (1969) who administered kanamycin and neomycin to five conditioned monkeys, and by Ylikoski et al. (1973) who examined conditioned guinea-pigs after the administration of gentamicin. One reason is surely the fact that the animals which are relatively easy to train for behavioural hearing determinations are usually not as suitable for cochlear microdissection and histological examination However Anderson and Wedenberg introduced in 1965 a relatively simple method for pure tone hearing testing in guinea-pigs, animals which are perhaps the best adapted for studies of cochlear pathology

Using the method of Anderson and Wedenberg for hearing measurements and the surface preparation technique (Retzius, 1884 Held 1902 Neubert 1950 Engström et al. 1964) for microscopic examination of the organ of Corti, we have

compared audiological results and cochlear pathology in guinea-pigs treated with various doses of gentamicin, kanamycin or neomycin for various lengths of time in an attempt to answer the following questions

1) What is the relation between the degree of hair cell injury and auditory sensitivity?
2) Is it possible to make a systematic investigation of frequency localization in the cochlea by allowing hearing loss to reach the desired cut-off frequency stopping the treatment at that point and correlating the extent of achieved hair cell loss with the final audiogram?

MATERIAL AND METHODS

Forty-two healthy young guinea-pigs, weighing at the beginning of the experiment 250–350 g, were used in the experiment. The animals were conditioned to respond to pure tone stimuli by the technique described elsewhere (Ylikoski et al., 1973) and the hearing threshold for frequencies 0.5 kHz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz 4 kHz, 8 kHz and 12 kHz was determined in each animal by the method introduced by Anderson and Wedenberg (1965). Most of the animals were monauralized by the surgical destruction of the left cochlea and retested after recovery

Then each animal was given gentamicin sulphate kanamycin sulphate or neomycin sulphate subcutaneously twice daily for various lengths of time. The dosage schedule is presented in Tables 1–3. All animals but one (K 4) were allowed to survive at least 10 days after the last injection and their hearing was tested until a stable threshold curve was obtained on three separate occasions. The survival time for each animal is shown in Tables 1–3

After the final audiogram the animals were anesthesized with chloroform, decapitated and the temporal bones were removed. The bulla was opened the stapes extracted, the round window membrane was opened and a small opening was made in the apex. The cochleas were perfused with 1 % or 2 % veronal-buffered osmium tetroxide and immersed in the fixation fluid for 1 hour 30 minutes. The specimens were then dehydrated in alcohol and embedded in Epon. Embedded cochleas were divided along the mid-modiolus with a 0.1 mm thick circular saw. Each half coil was cut into a block with a flat surface which included the whole cochlear duct. Each block containing a half coil was thinned and mounted on a glass slide basal membrane downwards (Ernstsson, 1971 1972). The specimens were studied through a water lens 40x with a Zeiss photomicroscope equipped with the interference contrast system (Nomarski 1955). The hair cells were counted and each cell marked as

CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
G10	GENTAMICIN	150mg/kg/day	5 days	13 days
G11			4	16
G12			6	18
G13			6	21
G14		30mg/kg/day	28	22
G15			28	24
G16			28	16
G17			28	16
G18			28	30
K10	KANAMYCIN	400mg/kg/day	6	15

Table 1 *Schedule of dosages and survival times for 10 guinea-pigs with unaltered hearing thresholds (Group I).*

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According to current knowledge, sound energy is converted into action potentials in the auditory nerve in the organ of Corti This process of transduction is generally considered to be carried out by the hair cells. In spite of the accumulation of more and more experimental and clinical data regarding the structural arrangement and the physiology of the organ of Corti there still exists a gap in the knowledge concerning the role of different types of hair cells in the transduction mechanism

Another generally accepted concept is that the cochlea functions not only as a transducer but also as a frequency and temporal analyzer According to the place principle points of maximal stimulation for each frequency are spatially arranged along the basilar membrane so that the area of optimal excitation for high frequencies is situated near the round window for the low frequencies the corresponding site is near the helicotrema If we accept that the place principle is functioning at least at higher frequencies, and that the hair cells are responsible for the auditory transduction then it would seem possible to study the specific role of different kinds of hair cells as well as the frequency localisation along the basilar membrane of the cochlea. This can be done by causing damage to a selected part of the cochlear partition and assessing the residual functional capacity of the cochlea by audiometric methods combined with microscopic examination of the organ of Corti.

A useful way of producing desired and selective damage inside the cochlea without causing mechanical injury or an intermixing of the cochlear fluids, is to administer ototoxic antibiotics whose effect can be quantified in terms of dosage and length of treatment. The ototoxic potentials of the useful but unruly family of basic streptomyces antibiotics" (Hawkins, 1959) was realized soon after their introduction and some of them were shown to possess a special cochleotoxic property

Although there is abundant data regarding the damage pattern in the cochlea after treatment with aminoglycoside antibiotics correlated to suprathreshold hearing measurements (pinnareflex in guinea-pigs, cochlear microphonics) there are still very few direct correlative studies between audiometric hearing threshold measurements and cochlear pathology The only studies of this kind published so far were carried out by McGee and Olzewski (1962) in four trained cats which had been treated with streptomycin and dihydrostreptomycin by McGee et al (1969) who studied one trained cat treated with gentamicin by Stebbins et al. (1969) who administered kanamycin and neomycin to five conditioned monkeys, and by Ylikoski et al. (1973) who examined conditioned guinea-pigs after the administration of gentamicin One reason is surely the fact that the animals which are relatively easy to train for behavioural hearing determinations are usually not as suitable for cochlear microdissection and histological examination. However Anderson and Wedenberg introduced in 1965 a relatively simple method for pure tone hearing testing in guinea-pigs, animals which are perhaps the best adapted for studies of cochlear pathology

Using the method of Anderson and Wedenberg for hearing measurements and the surface preparation technique (Retzius, 1884 Held 1902 Neubert 1950 Engström et al 1964) for microscopic examination of the organ of Corti, we have

compared audiological results and cochlear pathology in guinea-pigs treated with various doses of gentamicin, kanamycin or neomycin for various lengths of time in an attempt to answer the following questions

1) What is the relation between the degree of hair cell injury and auditory sensitivity?
2) Is it possible to make a systematic investigation of frequency localisation in the cochlea by allowing hearing loss to reach the desired cut-off frequency stopping the treatment at that point, and correlating the extent of achieved hair cell loss with the final audiogram?

MATERIAL AND METHODS

Forty-two healthy young guinea-pigs weighing at the beginning of the experiment 250–350 g, were used in the experiment. The animals were conditioned to respond to pure tone stimuli by the technique described elsewhere (Ylikoski et al., 1973) and the hearing threshold for frequencies 0.5 kHz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 8 kHz and 12 kHz was determined in each animal by the method introduced by Anderson and Wedenberg (1965). Most of the animals were monaurahzed by the surgical destruction of the left cochlea and retested after recovery

Then each animal was given gentamicin sulphate, kanamycin sulphate or neomycin sulphate subcutaneously twice daily for various lengths of time. The dosage schedule is presented in Tables 1–3. All animals but one (K 4) were allowed to survive at least 10 days after the last injection and their hearing was tested until a stable threshold curve was obtained on three separate occasions. The survival time for each animal is shown in Tables 1–3

After the final audiogram the animals were anesthesized with chloroform decapitated, and the temporal bones were removed. The bulla was opened the stapes extracted the round window membrane was opened, and a small opening was made in the apex. The cochleas were perfused with 1 % or 2 % veronal-buffered osmium tetroxide and immersed in the fixation fluid for 1 hour 30 minutes. The specimens were then dehydrated in alcohol and embedded in Epon. Embedded cochleas were divided along the mid-modiolus with a 0.1 mm thick circular saw. Each half coil was cut into a block with a flat surface which included the whole cochlear duct. Each block containing a half coil was thinned and mounted on a glass slide basal membrane downwards (Ernstsson, 1971, 1972). The specimens were studied through a water lens 40x with a Zeiss photomicroscope equipped with the interference contrast system (Nomarski 1955). The hair cells were counted and each cell marked as

CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
G10	GENTAMICIN	150mg/kg/day	5 days	13 days
G11			6	10
G12			8	18
G13			6	21
G14		50mg/kg/day	28	22
G15			28	24
G16			28	18
G17			28	18
G18			28	30
K10	KANAMYCIN	400mg/kg/day	6	15

Tabl 1 *Schedule of dosages and survival times for 10 guinea-pigs with unaltered hearing* s (Group I).

CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
N3	NEOMYCIN	250mg/kg/day	7 days	58 days
N4			7	38
N13			7	126
G19	GENTAMICIN	50mg/kg/day	29	30
G21		100mg/kg/day	21	43
G22	-		21	28
G24			16	32
G26			16	49
G28			10	35
G33			17	210
G35			17	14
GA14			11	14
K9	KANAMYCIN	400mg/kg/day	6	18
K12			7	135
K13			6	105
K19		200mg/kg/day	16	30
K21			18	64
K22			16	70
K23			16	112
K24			16	70

Table 2 *Schedule of dosages and survival times for 20 guinea-pigs with relatively abrupt hearing losses (Group II).*

CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
N11	NEOMYCIN	250mg/kg/day	7 days	105 days
N15			5	118
K4	KANAMYCIN	300mg/kg/day	12	4
K14		200mg/kg/d y	20	64
K15			20	27
G23	GENTAMICIN	100mg/kg/d y	18	90
G34			14	98
N5	NEOMYCIN	250mg/kg/day	8	98
N6			8	70
N7			8	91
N10			7	91
K11	KANAMYCIN	400mg/kg/day	8	15

Table 3 *Schedule of dosages and survial times for 12 guinea-pigs with flat hearing losses (Group III).*

"present" or "missing" in accordance with Engström et al. (1966) Ernstsson (1971 1972) Ylikoski et al. (1973) in a cytocochleogram. From this cochleogram the percentage of missing outer hair cells (OHCs) and inner hair cells (IHCs) per millimetre of cochlear length was calculated and plotted on a graph. Selected pieces from the mounted block were reoriented and remounted in Epon. The remounted specimens were used for 0.5–1 micron sections for light microscopy and for thin sections for electron microscopy

For a graphic presentation of the data both histological and audiological results were plotted on the same graph. The changes in hearing, in decibels, and the percentage of damaged hair cells in each millimetre segment were represented along the ordinate axis, the length in millimetre of the basilar membrane measured from the round window and the frequencies, on a logarithmic scale, were represented along the abscissa axis. The specific distance representative of each frequency in the graph was chosen on the basis of earlier studies (Békésy 1947 1960 Schuknecht 1953 Stebbins et al. 1969) and on our preliminary results (Ylikoski et al. 1973) which were as follows 12 kHz at 3 5 mm, 8 kHz at 5 0 mm, 4 kHz at 8 mm, 3 kHz at 9.5 mm, 2 kHz at 11 0 mm, 1 5 kHz at 12.5 mm, 1 kHz at 14 mm and 0.5 kHz at 17 mm.

RESULTS

Because the main aim of the present work was to induce hearing losses of various degrees which could be related to corresponding changes in morphology the results are presented according to the changes in hearing sensitivity The following groups were identified

1) *No change or slight elevation in hearing threshold*

This group included animals which revealed unaltered hearing sensitivity compared with pretreatment audiograms, or no more than a 10 dB deterioration at frequencies ranging from 0.5 kHz to 8 kHz, or no more than a 20 dB impairment at the highest frequency tested (12 kHz) In some cases elevations of the hearing threshold were observed during treatment, especially at the highest frequencies, but these returned to the pretreatment level soon after the administration of drugs was discontinued.

This group consisted of ten animals (G 10, 11 12, 13 14 15 16, 17 18 and K 10) Of these 5 animals were treated with a low dose of gentamicin for a long period (29 days) (G 14 15 16, 17 and 18) 4 animals (G 10 11 12 and 13) were treated with a high dose (150 mg) of gentamicin for a short period (5–6 days) and one animal (K 10) was given kanamycin 400 mg for 6 days (Table 1)

All animals except one (G 17) displayed preserved pinnareflex at the pretreatment level at the time of decapitation.

In spite of unchanged pure tone audiograms, all the animals displayed notable but, in most cases, slight hair cell damage which commonly was evenly distributed as a scattered loss of the OHCs over the entire cochlea. However in three cases there was a relatively severe loss of OHCs particularly in the basal coil (G 17 18 and K 10) (Fig. 1) G 18 showed an extensive

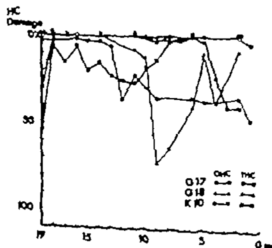


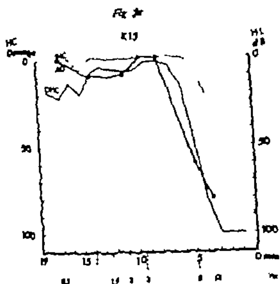
Fig. 1. The extent of hair cell damage in three animals that displayed unchanged pure tone audiograms after treatment with gentamicin 50 mg/kg for 29 days (G 17 and G 18) or kanamycin 400 mg/kg for 6 days (K 10).

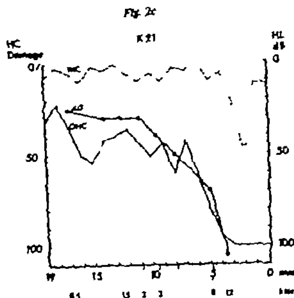
CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
N3	NEOMYCIN	250mg/kg/day	7 days	56 days
N4			7	39
N13			7	126
G19	GENTAMICIN	50mg/kg/day	28	30
G21		100mg/kg/day	21	43
G22	–		21	26
G24			16	32
G26			16	48
G28			10	35
G33			17	210
G35			17	14
GA14			11	14
K9	KANAMYCIN	400mg/kg/day	6	18
K12			7	139
K13			6	185
K18		200mg/kg/day	16	30
K21			16	64
K22			16	70
K23			16	112
K24			18	70

Table 2 *Schedule of dosages and survival times for 20 guinea-pigs with relatively abrupt hearing losses (Group II).*

CASE	DRUG	DOSE	DURATION OF TREATMENT	SURVIVAL TIME
N11	NEOMYCIN	250mg/kg/day	7 days	105 days
N15			5	119
K4	KANAMYCIN	300mg/kg/day	12	4
K14		200mg/kg/day	20	84
K15			20	27
G23	GENTAMICIN	100mg/kg/day	16	80
G34			14	88
N5	NEOMYCIN	250mg/kg/day	8	98
N6			8	70
N7			8	91
N10			7	91
K11	KANAMYCIN	400mg/kg/day	6	15

Table 3 *Schedule of dosages and survial times for 12 guinea-pigs with flat hearing losses (Group III).*





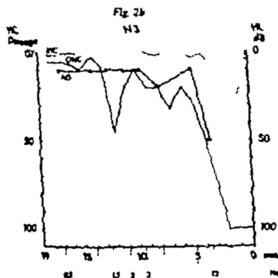


Fig. 2. The results of histological and audiological examinations in the three animals in group A whose hearing losses were the most abrupt. The changes in hearing in decibels, and the percentage of damaged hair cells in each mm segment are represented along the ordinate axis, the length in mm of the basilar membrane and the corresponding frequency are represented along the abscissa axis.

a) K 13 was given kanamycin 400 mg/kg for 6 days
b) N 3 was given neomycin 250 mg/kg for 7 days
) K 21 was given kanamycin 200 mg/kg for 16 days.

of the hearing threshold at 8 kHz and a 55 dB elevation at 12 kHz (Fig. 2c). Histopathological data disclosed a nearly total loss of OHCs in the extreme basal 5 mm area after which the OHCs remained in gradually increasing numbers so that at 9 mm only 45 % were missing. This damage of about 45 % extended up to 17 mm where there was some improvement. The IHCs were generally well preserved except at a point 2 mm from the round window where there was a loss of 50 %.

B) The second group of *three animals* (G 21 24 and K 12) was observed to *have quite similar hearing impairment* and histopathological changes. This is why they are presented as one group *(Fig. 3)*. The hearing was normal or nearly normal at lower frequencies up to 2 kHz. At 3 kHz it clearly deteriorated (about 30 dB) and at higher frequencies deterioration increased further (about 40 dB). A histopathological examination revealed an almost total loss of OHCs in the basal 9 mm region

OHC loss of up to 70 % in a narrow region 7 mm to 9 mm from the basal end The IHCs were intact in the cochlea of every animal except one (K 10) which revealed a degeneration in the apex of about 30 %

II) Abrupt hearing loss

Relatively abrupt hearing loss was considered to be induced when the threshold shift was at least 30 dB over a frequency range of one and one-half octaves. This experimental group consisted of 19 animals which were given various antibiotics for different periods of time and in varying dosages as follows 3 animals were treated with neomycin (250 mg/kg) for seven days (N 3 N 4 N 13) 8 animals were given gentamicin (100 mg/kg) for between 10 and 21 days (G 21 22 24 26 28 33 35 and GA 14), one animal was given gentamicin (50 mg/kg) for 29 days (G 19) 3 animals were treated with kanamycin (400 mg/kg) for 6–7 days (K 9 12 and 13) and 5 animals were given kanamycin (200 mg/kg for 16 days (K 19 21 22 23 and 24) (Table 2)

The hearing loss was generally observed initially as a high tone loss with the elevation slowly shifting towards the lower frequencies until all frequencies above 2 kHz were involved This was the borderline because there were no cases where the abrupt threshold shift or cut-off frequency" was observed at a lower level than 2 kHz (Those animals in which the hearing was observed to continue to deteriorate weeks after the cessation of treatment until deafness with a flat curve resulted were not included in this group)

Some of these animals can be grouped into sub-groups on the basis of the similarity of hearing changes and associated hair cell pathology

A) The first group comprises three animals (K 13 K 21 and N 3) of which two had abrupt high tone losses and relatively sharply demarcated hair cell injuries located below the 7 mm level. K 21 was placed in this group because it showed a sharp transition from total OHC degeneration to 50 % damage within the same level of the cochlea, although the OHCs of the first row were missing as high up as the apex.

1) K 13 exhibited an audiogram with unchanged hearing at 4 kHz (Fig. 2a) At 8 kHz there was a drop of 60 dB and at 12 kHz the hearing was further impaired by 20 dB for a total drop of 80 dB compared with the pretreatment audiogram An histological examination disclosed that the OHCs were totally missing in the basal 4 4 mm along the basilar membrane and the IHCs were almost totally absent in the basal 3 mm area with a sharp transition to a nearly normal hair cell pattern within 2.5 mm of the cochlear length.
2) N 3 displayed a 10 dB loss at lower frequencies up to a frequency of 8 kHz with an abrupt shift of 40 dB for a total of 50 dB at 12 kHz (Fig 2b) Correspondingly all the OHCs were missing in the lowermost 3 mm along the basilar membrane but more than 50 % were present at the 4 mm point and about 80 % remained at 6 mm beyond which there was a loss of about 30 % until the 14 mm level where the cellular pattern was almost intact There was a 25 % loss of IHCs at the 2 mm point in other areas the IHC-pattern was nearly normal.

   Both of these animals which experienced a relatively abrupt high tone loss and a sharp transition from total sensory cell loss to an almost normal pattern were given large doses of antibiotics for a short time – for the former (K 13) 400 mg/kg kanamycin for 6 days for the latter (N 3) 250 mg/kg neomycin for 7 days. The changes, however resemble those observed by Stebbins et al (1969) when they used very small doses on monkeys for a long period of time (several hundred days)
3) K 21 displayed a 30 dB loss at lower frequencies in the range 0 5 kHz to 2 kHz whereafter there was a 20 dB shift at 4 kHz and a further 20 dB elevation

tem was observed at the 15 mm point. In G 28 and G 35 the IHCs had suffered damage only in the hook region. In G 26 there was a total loss of IHCs up to the 7 mm level and the whole organ of Corti had disappeared in many places in the same area.

D) The following three animals K 22, K 24 and K 19 were given 200 mg/kg kanamycin for 16 days and this treatment induced an almost equal hearing impairment in each of them (Fig. 5) There was an average 20–30 dB loss in the lower frequency range up to 2 kHz, then a rather steeply sloping shift so that the elevation of the hearing threshold was about 50 dB at the frequency of 3–4 kHz 70 dB at 8 kHz and 80 dB at 12 kHz. The histopathological data disclosed extensive sensory cell damage in each cochlea. The OHCs were virtually missing basally on the average up to the 8 mm point beyond which more and more OHCs remained, but there was a pronounced loss, about 20–30 %, extending to the apex. The IHCs were severely injured in K 22. They as well as the whole organ of Corti were absent in the lowermost 5 mm along the basilar membrane. After this point there was a 50 % degeneration of IHCs up to 8 mm from the round window K 24 experienced only a 50 % injury to the IHCs in the extreme basal end up to 3.5 mm. K 19 exhibited the slightest IHC-damage of this group and then only in the hook area where it did not exceed 30 %

E) N 4 demonstrated a relatively slight elevation of the hearing threshold 40 dB at the frequency of 12 kHz and 20 dB at frequencies from 8 kHz to 3 kHz and 10 dB at lower frequencies (Fig. 6) This was related to histological changes which revealed an almost total OHC loss in the basal 6 mm region followed by about 50 % damage up to the 11 mm level beyond which only the first row of OHCs were missing up to 17 mm along the cochlea. The IHCs were generally well preserved. About 25 % were absent in the hook region, then intact to the 17 mm point where in spite of the well preserved OHCs, almost all IHCs were missing to the apex.

F) The following two animals, N 13 and G 33 were found to have almost similar hearing losses (Fig. 7) N 13 had received neomycin 250 mg/kg for as many days as N 4 but disclosed very

Fig. 6

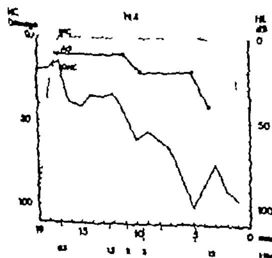


Fig. 6 The results of audiological and histological examinations in one animal (N 4) given neomycin 250 mg/kg for 7 days.

Fig. 7

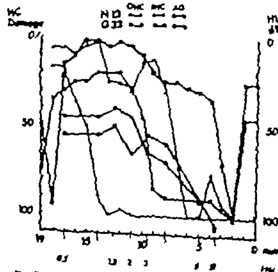
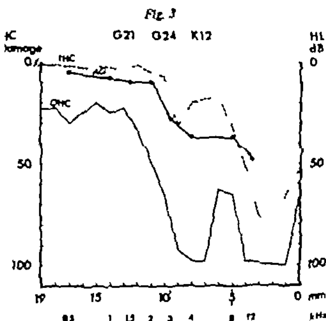


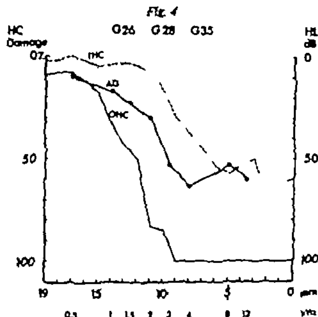
Fig. 7 Extent of audiological and sensory cell damage suffered by N 13, given neomycin 250 mg/kg for 7 days and by G 33, given pentamicin 100 mg/kg for 17 days.

along the cochlea after which the damage gradually lessened to a nearly normal OHC-pattern within 3–4 mm In K 12 however the first row of OHCs was missing to the apex

In G 24 and K 12 there was a complete loss of IHCs in the extreme basal 3 mm region. This loss was associated with a degeneration of the whole organ of Corti G 21 exhibited about 50 % damage to the IHCs at the corresponding level with the IHCs reaching nearly normal preservation within 2–4 mm in the apical direction from this 3 mm point

C) The animals G 26 G 28 and G 35 were grouped together because they also showed rather similar hearing losses. The average audiogram of this group revealed a slight elevation of the hearing threshold at 0.5 kHz and 1 kHz (10–20 dB) which further deteriorated at higher frequencies, the loss being 30 dB at 2 kHz and 65 dB at 4 kHz (Fig. 4) At 8–12 kHz it was somewhat better 50–60 dB In the histopathological examination extensive damage was observed to the OHCs which were totally missing in the basal coil of each cochlea the average nearly total loss of the OHCs extending up to the 10 mm point along the basilar membrane An almost normal OHC pat





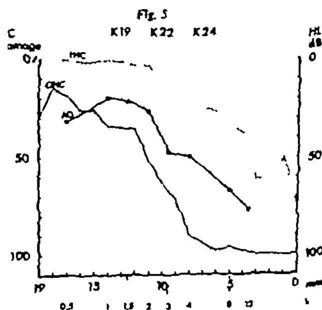


Fig. 3. Mean values of hearing-threshold elevation and hair cell damage in three animals with abrupt hearing losses (group II B). G 21 had been given gentamicin 100 mg/kg for 21 days and G 24 for 16 days, K 12 was given kanamycin 400 mg/kg for 7 days.

Fig. 4. Mean values of hearing-threshold elevation and hair cell damage in three animals with abrupt hearing losses (group C). All these animals had been given gentamicin 100 mg/kg, G 26 for 16 days, G 28 for 10 days and G 35 for 17 days.

Fig. 5. Mean values of hearing-threshold elevation and hair cell damage in three animals with abrupt hearing losses (group D). All of these animals (K 19 K 22, and K 24) were given kanamycin 200 mg/kg for 16 days.

tern was observed at the 15 mm point In G 28 and G 35 the IHCs had suffered damage only in the hook region. In G 26 there was a total loss of IHCs up to the 7 mm level and the whole organ of Corti had disappeared in many places in the same area.

D) The following three animals K 22, K 24 and K 19 were given 200 mg/kg kanamycin for 16 days and this treatment induced an almost equal hearing impairment in each of them (Fig. 5). There was an average 20–30 dB loss in the lower frequency range up to 2 kHz, then a rather steeply sloping shift so that the elevation of the hearing threshold was about 50 dB at the frequency of 3–4 kHz, 70 dB at 8 kHz and 80 dB at 12 kHz. The histopathological data disclosed extensive sensory cell damage in each cochlea. The OHCs were virtually missing basally on the average up to the 8 mm point beyond which more and more OHCs remained, but there was a pronounced loss, about 20–30 % extending to the apex. The IHCs were severely injured in K 22. They as well as the whole organ of Corti were absent in the lowermost 5 mm along the basilar membrane. After this point there was a 50 % degeneration of IHCs up to 8 mm from the round window. K 24 experienced only a 50 % injury to the IHCs in the extreme basal end up to 3.5 mm. K 19 exhibited the slightest IHC-damage of this group and then only in the hook area where it did not exceed 30 %.

E) N 4 demonstrated a relatively slight elevation of the hearing threshold 40 dB at the frequency of 12 kHz and 20 dB at frequencies from 8 kHz to 3 kHz and 10 dB at lower frequencies (Fig. 6). This was related to histological changes which revealed an almost total OHC loss in the basal 6 mm region followed by about 50 % damage up to the 11 mm level beyond which only the first row of OHCs were missing up to 17 mm along the cochlea. The IHCs were generally well preserved. About 25 % were absent in the hook region then intact to the 17 mm point where, in spite of the well preserved OHCs, almost all IHCs were missing to the apex.

F) The following two animals, N 13 and G 33 were found to have almost similar hearing losses (Fig. 7). N 13 had received neomycin 250 mg/kg for as many days as N 4 but disclosed very

Fig. 6

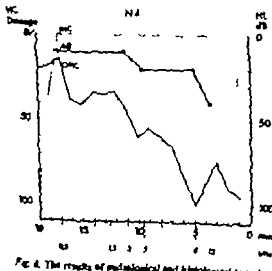


Fig. 6. The results of audiological and histological examinations in one animal (N 4) given neomycin 250 mg/kg for 7 days.

Fig. 7

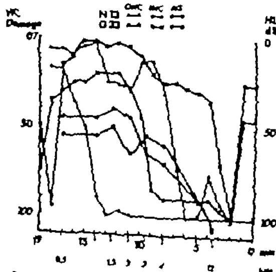
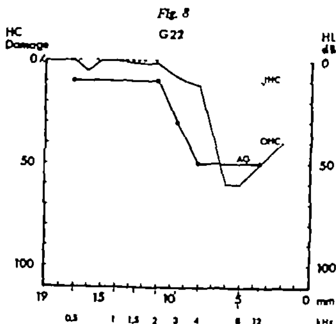
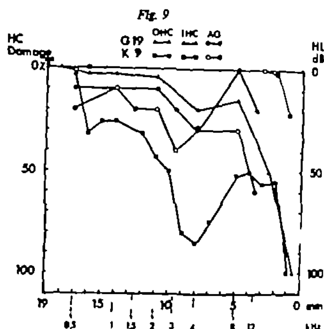


Fig. 7. Extent of audiological and sensory cell damage suffered by N 13, given neomycin 250 mg/kg for 7 days and by G 33, given gentamicin 100 mg/kg for 17 days.





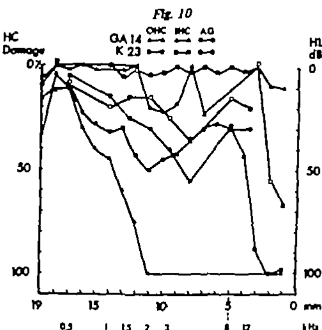


Fig. 8. The results of audiological and histological examinations in G 22 given gentamicin 100 mg/kg for 21 days.

Fig. 9. Extent of audiological and sensory cell damage in G 19 given gentamicin 50 mg/kg for 29 days, and in K 9 given kanamycin 400 mg/kg for 6 days. The audiogram of G 19 dips at 4 kHz, that of K 9 dips at 3 kHz.

Fig. 10. Results of audiological and histological examinations in GA 14 given gentamicin 100 mg/kg for 11 days, and K 23, given kanamycin 200 mg/kg for 16 days. Both animals displayed a "dip" in their audiograms at 4 kHz.

poor hearing after treatment It had deteriorated 40–45 dB at lower frequencies from 0.5 kHz to 2 kHz and the hearing sensitivity dropped steeply at higher frequencies to the 70 dB level at 3–4 kHz and to the 90 dB level at 8–12 kHz Correspondingly all the hair cells as well as the organ of Corti had practically disappeared in the basal 6 mm area along the basilar membrane after which there was an approximate 25 % injury to the IHCs until 13 mm Almost all the OHCs were missing up to 14 mm region of the cochlea.

Although G 33 showed a similar hearing capacity as N 13 the histopathological data of the cochlea was more related to the previously presented cases of gentamicin injury in groups B and C with the difference that in G 33 the IHCs were largely missing in the uppermost 2 mm area of the cochlea. G 33 was the only animal treated with gentamicin in which this apical IHC degeneration was revealed

G) G 22 displayed a flat hearing loss of 10 dB at lower frequencies up to 2 kHz whereafter there was a drop of 40 dB at both 4 kHz and at higher frequencies tested (Fig. 8) Microscopic examin-

ation demonstrated remarkably less damage to the hair cells than in other animals with corresponding hearing impairments. The IHCs were almost intact in the entire cochlea and the OHCs had suffered only about 50 % damage in the lowermost 6 mm along the length of the cochlea.

II) G 19 K 9 GA 14 and K 23 formed a group which had in common a dip in the hearing threshold at 3–4 kHz and which had somewhat better hearing at higher frequencies. The abruptness of hearing changes in this group did not fill the demands mentioned above

1) G 19 showed a slight hearing impairment with a 10 dB loss at 2 kHz and lower frequencies and a 20 dB dip at 4 kHz followed by a 30 dB improvement at 8 kHz (Fig. 9)
The organ of Corti of this animal had suffered the following damage all the OHCs were absent from the basal end to 1.5 mm about 30 % were missing at the 4 mm point from the round window after which about 20 % were missing up to the 9 mm point. The IHCs were intact in the whole cochlea.

2) K 9 had a greater hearing impairment with a general 10–20 dB hearing loss which increased by 20 dB at 2 kHz. Its hearing was 10 dB better at 4 kHz and 8 kHz with, however a 30 dB dip at 1? kHz. Cochlear histopathology revealed a ?0 % injury to IHCs in the round window area. The OHCs were completely missing in the lowermost 1.5 mm from where there was an average of 50 % damage until the 17 mm level. There was a "notch" with about 85 % damage between 7 mm and 9 mm possibly corresponding to the functional dip in the audiogram

3) K 23 had a general 20 dB hearing deterioration at all frequencies plus a ?0 dB dip at 4 kHz (Fig. 10) Microscopic examination disclosed relatively severe damage About 60 % of the IHCs were missing in the hook area, but elsewhere they were almost intact. The OHCs totally disappeared in the basal 2.5 mm region of the cochlear duct, and about 50 % were missing up to the 11 mm point after which the first row of OHCs was defective up to 16 mm.

4) The audiogram of GA 14 showed an evenly descending curve from a frequency of 0.5 kHz to 4 kHz where the hearing loss was 55 dB At two higher frequencies there was some hearing improvement with only a 30 dB loss. Cochlear histopathology demonstrated a maximum of 20 % damage in the IHC-pattern but the OHCs were totally destroyed up to the 11 mm level and partially damaged to the 16 mm point.

III) *Hearing loss with a flat curve*

A) This group consisted of five animals (N 5 6, 7 10 and K 11) which all demonstrated similar hearing losses with about a 30–60 dB drop at each frequency (Fig. 11) The histological examination of the cochlea showed severe damage to the OHCs which were often present only in the most apical part of the cochlea. The IHCs were sometimes also severely degenerated in some areas along the cochlear duct. There were *large variations* in the extent of histological damage

B) This group contained seven animals, some from each antibiotic group (K 4 14 15 N 11 15 G 23 and 34). It was usually possible to distinguish them from the other animals already during treatment due to an extensive deterioration in hearing sensitivity which occurred at a very early stage. The hearing impairment continued to increase in some cases weeks after the cessation of the treatment. The common characteristic of this group was a nearly flat audiogram with a general 80–90 dB hearing loss at all frequencies (Fig. 12) This resembles one group of patients with ototoxic hearing loss described by Rosal et al. (1961) Cochlear histopathology revealed a severely damaged cochlea in all animals. Total disappearance of the sensory cells from the entire cochlea was, however never pro-

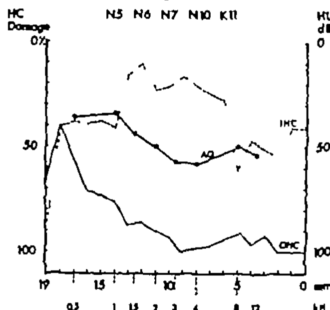


Fig. 11. Mean values of hearing-threshold elevation and hair cell damage in five animals that suffered flat hearing loss. N 5, N 6 and N 7 were given neomycin 250 mg/kg for 8 days and N 10 for 7 days, K 11 received kanamycin 400 mg/kg for 6 days.

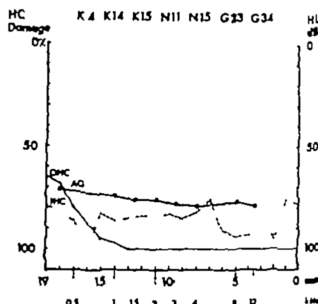


Fig. 12. Mean values of hearing-threshold elevation and hair cell damage in seven animals that suffered flat hearing loss and nearly total destruction of the organ of Corti. K 4 was given kanamycin 300 mg/kg for 12 days, K 14 and K 15 kanamycin 200 mg/kg for 20 days; N 15, neomycin 250 mg/kg for 5 days and N 11 for 7 days, and G 23 and G 24 gentamicin 100 mg/kg for 16 days.

duced there were always at least some OHCs left in the uppermost part of the cochlea. In one animal (K 15) all the IHCs had disappeared and in two others there were only six (G 34) and four (K 14) IHCs left. In all of these profusely destroyed cochleas, the supporting structures also revealed significant damage and in many places in the basal coil the entire organ of Corti had disappeared and had been replaced by a layer of flattened epithelium. The supporting elements, especially pillar cells, were, however, usually relatively well preserved from about the 8 mm point along the basilar membrane upwards in spite of complete hair cell degeneration.

DISCUSSION

A) The anatomical frequency scale

In the abrupt hearing loss group II there were 12 animals which exhibited a relatively distinct change in hearing sensitivity at a narrow frequency range (within one octave or one and one-half octave) and they had correspondingly relatively restricted lesions along the basilar membrane with a rather sharp transition from total destruction of the OHCs to a nearly normal pattern. These changes, however, were generally much less distinct than those reported by Stebbins et al. (1969) in four monkeys. However, the data obtained seems to be reliable enough to permit some conclusions regarding the spatial arrangement of frequency localisation on the cochlear duct.

The audiogram of N 3 (Fig. 2b) showed an abrupt loss of hearing at 12 kHz. An histopathological examination of the cochlea revealed a total loss of OHCs and some of the IHCs to the 3 mm point from the basal end beyond which the sensory cells were better preserved so that at the level of 4 mm the IHCs were intact and more than 50% of the OHCs remained. From this one can conclude that the area of maximum excitability for 12 kHz lay below

the 4 mm point, and for 8 kHz above the 3 mm point. Thus the area from 3 mm to 4 mm from the basal end of this cochlea was between the regions of optimal excitability for frequencies between 8 kHz and 12 kHz.

Guinea-pig K 13 (Fig. 2a) had normal hearing at lower frequencies up to 4 kHz with an abrupt threshold shift at 8 kHz. Cochlear histopathology disclosed an almost total loss of the OHCs up to the 4.4 mm point after which a rapid transition to an intact cellular pattern took place within 2.5 mm. It was reasonable to assume that the region of maximum excitability for 8 kHz was located below the 7 mm point, and that for 4 kHz it was located from the 4.4 mm region towards the apex. Thus it follows that the area between 4.4 mm and 7 mm from the round window corresponds to the area between the points of maximal stimulation of frequencies between 4 kHz and 8 kHz.

The audiological examination of K 21 (Fig. 2c) revealed an abrupt 40 dB threshold shift between the frequencies of 3 kHz and 8 kHz. The histological examination of the cochlea showed a nearly complete loss of the OHCs up to the 5 mm level beyond which there was a transition towards a better preserved area so that at the 9 mm point only 45% of the OHCs were degenerated. This should account for the hearing loss of less than 50 dB (Schuknecht 1953, Bredberg, 1968). This in turn would mean that the area of maximal stimulation for 8 kHz was situated below the 9 mm point and for 3 kHz upwards from the 5 mm point towards apex. It can, therefore, be concluded that the region between 5 mm and 9 mm along the basilar membrane was connected to the areas of maximal stimulation for frequencies between 3 kHz and 8 kHz.

The average audiogram of group II/B (Fig. 3) showed a 40 dB shift in hearing sensitivity between the frequencies of 2 kHz and 4 kHz. The histological examinations revealed that the OHCs were almost entirely missing up to the 9 mm level beyond which there was a transition towards the normal cellular pattern so that at

AREA BETWEEN mm	CASE	FREQUENCIES
3 – 4	M3	12–8 kHz
4.4 – 7.0	K13	8–4 kHz
5 – 9	K21	8–3 kHz
9 – 12	II B	4–2 kHz
9 – 14	II C	4–2 kHz
9 – 12	II D	4–2 kHz

Table 4. *The data obtained from 12 animals with abrupt hearing loss on which the frequency analysis (Fig. 13) is based. On the left are given the segments of the basilar membrane we examined and which are thought to be related to the range of frequencies given on the right. Groups II B, C and D represent the mean values of three guinea-pigs with similar audiological and histological impairment. Group II B includes guinea-pigs G 21, G 24 and K 12, group II C, G 26, G 28 and G 35, group II D, K 19, K 22 and K 24.*

the 12 mm level only 25% of the OHCs were absent. From this it was clear that the area of maximal excitation for 2 kHz was above the 9 mm point, and for 4 kHz below



Fig. 13. Frequency analysis based on data in Table 4 plotted so that the frequencies are presented along the abscissa axis and the length, in millimetres, of the basilar membrane measured from the round window are presented along the ordinate axis. The six rectangles represent the animals studied.

the 12 mm point Thus the area between 9 mm and 12 mm from the base of this cochlea should correspond to the area between the points of optimal stimulation for frequencies between 2 kHz and 4 kHz

Similar audiological changes were obtained in groups II/C (Fig. 4) and II/D (Fig. 5) and these were related to the absence of the OHCs up to the 9 mm region for the former and up to the 8 mm region for the latter The upper margin of the transitional region for the two groups were respectively the 14 mm point and the 12 mm point.

The data for the above analysis is shown in Table 4 and in figure 13 in which the distance along the basilar membrane is plotted as a function of frequency Frequency is represented along the ordinate on a logarithmic scale with the assumption that the upper limit of frequency sensitivity for the guinea pig cochlea lies at about 32 kHz.

B) Correlation between hair cell damage and hearing sensitivity

Although there is some difference of opinion regarding the roles of various types of hair cells in the cochlear function (Ward & Duvall 1971 Lynn & Sayers 1970 Billone & Raynor 1973) there is considerable data indicating that the OHCs alone are responsible for the transduction of auditory stimuli near the threshold and the IHCs for higher intensities (Lurie 1937 Schuknecht 1953 Bredberg 1968 Dallos et al 1972) If we also take into account the orderly arrangement of frequency responses along the cochlear duct based on the large amount of physical, physiological and morphological evidence both in humans and in experimental animals (Growe et al. 1934 Stevens et al. 1935 Davis et al. 1949 Bekesy 1947 1960 Schuknecht 1953b Johnstone et al. 1970 Stebbins et al 1969) several interesting observations can be made from the above results.

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Groups II and III

All animals included in these groups displayed impaired hearing which in some animals was relatively abrupt and therefore it was possible to correlate hearing impairment with a rather restricted change in the cytocochleogram and thus to use the correlation in the investigation of frequency distribution along the cochlear duct. For correlation studies between hair cell injury and hearing loss all the animals of these two groups were used

On the basis of the previously given frequency map the percentage of sensory cell degeneration at each millimetre point was related to a corresponding hearing loss in decibels. The results of this correlation are illustrated in the accompanying Table 5 where the animals are grouped according to the degrees of hair cell damage as follows

I) All the sensory cells degenerated. This group included all the cases where at least 80% of both the IHCs and the OHCs were missing in the corresponding cochlear region Supporting structures were variably affected with the complete disappearance of the organ of Corti in some areas to those with well preserved pillar cells in others. The average hearing loss resulting from this nearly total loss of sensory cells was 79 dB and there were no significant differences between the hearing results at higher or lower frequencies.

How valid our hearing test method in measuring such high intensity tones is

HC	DAMAGE	FREQUENCY kHz								MEAN HEARING
		12	8	4	3	2	1 5	1	0 5	LOSS dB
IHC	80–100% Deg	80	82	82	83	81	80	74	68	78
OHC	80–100% Deg	(9)	(8)	(4)	(5)	(5)	(5)	(7)	(4)	(47)
IHC	11 79% Deg	67	55	57	60	54	50	35	60	55
OHC	75–100% Deg	(13)	(11)	(13)	(10)	(7)	(3)	(2)	(1)	(80)
IHC	< 11% Deg	48	40	50	38	35	47	45		42
OHC	75–100% Deg	(4)	(5)	(7)	(5)	(2)	(3)	(3)		(29)
IHC	< 11% Deg	51	49	35	38	21	20	17	–	38
OHC	40– 74% Deg	(4)	(6)	(3)	(8)	(11)	(7)	(3)		(42)
IHC	< 4% Deg	20	10	25		10	20	20	18	18
OHC	20– 39% Deg	(1)	(1)	(2)		(1)	(7)	(8)	(4)	(25)

( ) Number of observations

Table 5 *Relationship between various degrees of hair cell damage and subsequent hearing losses at various frequencies.*

is not clear Whether the animals are really responding to the sound waves or to the air vibrations produced by these high-intensity tones, is a question that cannot be answered here. However responses to air vibrations seem rather likely especially in the group of animals which had almost total hair cell destruction in the entire cochlea (group III/B) (Schuknecht, 1953b)

2) All the OHCs degenerated (75–100%) and a portion of the IHCs (11% to 79%) degenerated In these cases there were probably no functioning OHCs and the damage to the IHCs varied greatly The average hearing loss for this group was 55 dB which shows that even a relatively few preserved IHCs (21%) appear to improve hearing capacity remarkably On the other hand a relatively well preserved IHC-pattern (89% left) cannot account for better hearing if all the OHCs are degenerated.
3) All the OHCs degenerated (75–100%), less than 11% of the IHCs degenerated. This group showed an average hearing loss of 42 dB This therefore, indicates the degree of hearing impairment when all the OHCs are missing but the IHCs are almost intact.
4) OHC-degeneration from 40% to 74%, IHC-degeneration less than 11%. The average hearing loss was 38 dB *which* corresponds to the condition when the *first and* second row of the OHCs are degenerated but the third is preserved.
5) OHC-degeneration from 20% to 39% The average hearing loss was 18 dB *which corresponds* to the condition when only the first row of the OHCs is missing.

The neomycin-treated animals *that* exhibited total IHC-degeneration (Figs. 6 and 11) *with about 50% damage to the OHCs* (In one case, N 4 there was an OHC degeneration of about 25%) had a hearing deterioration that was apparently related to the OHC damage. The apical IHC loss does *not usually* seem to have any influence on auditory sensitivity although opposite results have been reported elsewhere (Stebbins et al. 1973)

In earlier papers, where a correlation has been made between auditory impairment and sensory cell damage, *it* has been cus-

the 12 mm point Thus the area between 9 mm and 12 mm from the base of this cochlea should correspond to the area between the points of optimal stimulation for frequencies between 2 kHz and 4 kHz

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IHC 80-100% Deg OHC 80-100% Deg	80 (9)	82 (8)	82 (4)	83 (5)	81 (5)	80 (5)	74 (7)	68 (4)	79 (47)
IHC 11-79% Deg OHC 75-100% Deg	67 (13)	55 (11)	57 (13)	60 (10)	54 (7)	50 (3)	35 (2)	60 (1)	55 (60)
IHC < 11% Deg OHC 75-100% Deg	48 (4)	40 (5)	50 (7)	38 (5)	35 (2)	47 (3)	45 (3)		42 (20)
IHC < 11% Deg OHC 40-74% Deg	51 (4)	48 (6)	35 (3)	36 (8)	21 (11)	20 (7)	17 (3)	-	38 (42)
IHC < 4% Deg OHC 20-39% Deg	20 (1)	10 (1)	25 (2)		10 (1)	20 (7)	20 (8)	18 (4)	18 (25)

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Table 5 *Relationship between various degrees of hair cell damage and subsequent hearing losses at various frequencies.*

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   How valid our hearing test method in measuring such high intensity tones is

Statistical comparison

Hearing loss seemed to be a function of hair cell loss involving both OHCs and IHCs. When data for all the animals which had suffered hearing loss (group II and III) were pooled, a statistically significant relationship between hearing loss and hair cell loss was evident. The correlation coefficient was computed for the percentage loss of both OHCs and IHCs per millimetre of each segment of the basilar membrane thought to be representative of each frequency and the hearing threshold at each frequency tested. The correlation coefficient between the percentage loss of OHCs and the corresponding hearing level was 0.735 which is statistically significant ($p < 0.001$)

GENERAL SUMMARY

To study and compare the degenerative changes in the cochlear hair cells of the guinea-pig after administration of gentamicin, kanamycin and neomycin, 94 guinea-pigs were treated with various doses of one of these antibiotics for various lengths of time. After survival times of from 0 days to 10 months the animals were decapitated and the pathological changes in the temporal bone were studied by light and electron microscopy. Complete cochleograms were constructed for the 68 guinea-pigs that survived to decapitation.

Selected cochlear segments in which some hair cell damage was apparent were chosen for a detailed study of both sensory cell and neural damage and for an evaluation of the relationship between the two.

Before administration of the drugs, 42 of the 94 guinea-pigs were conditioned to pure-tone hearing tests according to the technique of Anderson and Wedenberg (1965). The animals were then monaurilized and new hearing tests were performed after their recovery from this procedure. Cochlear damage was induced by administration of the ototoxic antibiotics and when a stable post treatment hearing threshold had been obtained, the animals were decapitated for studies of pathological changes in the temporal bone.

The earliest ultrastructural signs of degeneration, regardless of the antibiotic administered were observed in the outer hair cells of the basal coil. Disarrangement of the double membranes along the sides of these cells was evident and dark inclusion bodies appeared in their subcuticular cytoplasm. At later stages the interspaces between the flattened membranes become distended leading to vacuolization of the sides of the cells and finally with the rupture of the plasma membrane and expulsion of the cellular organelles into the Nuel's space, to the cells' complete disintegration.

At an early stage of degeneration, swellings, presumably swollen afferent nerve endings and dendrites, were occasionally seen below the inner hair cells.

The pattern of damage induced by the three antibiotics differed. Neomycin seemed to attack the hook area and the apical coil first, whereas gentamicin and kanamycin, at first, usually destroyed the outer hair cells in the upper basal coil and in the hook simultaneously. Neomycin also displayed a clearcut affinity for attacking the inner hair cells of the apex, cells seldom damaged after administration of gentamicin or kanamycin. The extent of the lesion affecting the outer hair cells was generally rather widespread. Thus the area along the cochlea between a nearly normal population of outer hair cells and complete loss of such cells was usually broader in animals treated with kanamycin than in those treated with gentamicin.

Our results demonstrate that great variations exist among individual animals as regards the effect of ototoxic antibiotics. The degree of damage by such drugs to the organ of Corti cannot therefore be quantified in terms of dosage but must be assessed by examining the hair cell population of each animal individually. Furthermore, because of the delayed effect of basic aminoglycoside antibiotics, experimental animals must be allowed to survive at least three weeks after the cessation of treatment if correlative studies between

tomary to express this correlation as good if the hearing loss has been found to be related to a significant loss of hair cells in the frequency optimal response region in the cochlea (McGee & Olzewski, 1962 Elliot 1961 1965 Bredberg 1968 Stebbins et al. 1969 Pinheiro et al 1973 Ylikoski et al 1973)

Yet in almost all studies of this kind there have been animals which have not fullfilled this criterion. Explanations for the inconsistency between audiological and histological changes have then been sought elsewhere in the cochlea or in the higher auditory pathways. In some cases there have been hearing losses which have had no corresponding damage in the cytocochleogram (Bredberg, 1968) The explanation has been looked for at the ultrastructural level where significant changes have been found in the receptor poles of the hair cells (loss or clumping of the stereocilia, giant hairs) (Lundquist & Wersäll, 1971 Bredberg, 1972) or in the cell body interfering with the cell metabolism (Lundquist & Wersäll, 1966 1967) or yet again in some cases in the synaptic regions (Spoendlin 1972) Primary changes have also been found in the spiral ganglion (Floberg et al 1949 Kellerhals et al. 1967) and in the cochlear nuclei (Stebbins et al. 1969 McGee & Olzewski, 1962)

In our material, two animals displayed a more severe hearing loss than could have been expected from the cytocochleogram Both these cases (G 22 and G 33) revealed significant degeneration of sensory cells although not to the extent observed in other animals with corresponding hearing losses. An electron microscopic examination of the cochleas did not reveal an explanation for this deviation but other factors, such as individual variations and possible damage in the higher levels of the auditory system can easily account for the differences.

A more complicated situation arises where an animal has extensive damage in the sensory and nervous elements in a relatively wide area of the cochlea but still experiences normal or nearly normal hearing. Such reports were published both by Eldredge and Miller (1969) concerning one chinchilla which exhibited severe hair cell damage but only a 20 dB hearing loss, and by Ward and Duvall (1971) in another chinchilla which displayed normal hearing in spite of the complete loss of the OHCs in the first and in part of the second turn. In these cases, two explanations have been offered

1) The animals are hearing by means of the hair cells surviving in the areas outside the maximal response point due to the widening of the area of maximal excitation when the intensity is increased.
2) The IHCs alone are responsible for auditory sensitivity

Our results generally showed a good correlation between audiological and histological changes. Thus a severe degeneration of the OHCs in the basal half of the cochlea produced a hearing loss of 40–50 dB in frequencies above 2 kHz. When both the OHCs and IHCs were severely damaged in the basal coil the hearing loss was correspondingly more severe As mentioned above there were two animals which revealed a more pronounced hearing loss than could be interpreted from the cytocochleograms alone. On the other hand, two groups of animals exhibited better hearing than expected Some of the animals belonging to group I (G 17 G 18 and K 10) displayed a moderate loss of the OHCs in the upper basal coil but still exhibited normal hearing. This is difficult to explain but it seems likely that the pure tone audiogram is not a sensitive index for low level OHC pathology in a limited region. Another group of animals with an almost total loss of sensory elements (group III/B) still responsed to delivered tones averaging 80 dB This result can be explained either by the presence of preserved OHCs in the apical 2 mm region or by the possibility that the response was perceived not by the ears but that the animals responded to tactile vibration stimuli in their footpads, body hairs or whiskers at high stimulus intensities.

Statistical comparison

Hearing loss seemed to be a function of hair cell loss involving both OHCs and IHCs. When data for all the animals which had suffered hearing loss (group II and III) were pooled, a statistically significant relationship between hearing loss and hair cell loss was evident. The correlation coefficient was computed for the percentage loss of both OHCs and IHCs per millimetre of each segment of the basilar membrane thought to be representative of each frequency and the hearing threshold at each frequency tested. The correlation coefficient between the percentage loss of OHCs and the corresponding hearing level was 0.735 which is statistically significant ($p < 0.001$)

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function and morphological changes are to be made.

A partial or total loss of outer hair cells alone in a given segment of the cochlea, was not associated with any corresponding rarefaction or loss of neurons. When the inner hair cells had degenerated as well the number of neurons in the spiral ganglion and spiral osseous lamina was markedly reduced provided the survival time was long enough for degeneration to have run its course In the latter specimens 10–25% of the fibres in the spiral osseous lamina and about 30% of the cells in the spiral ganglion survived The majority of these preserved neurons appeared normal by electron microscopy although the relative number of unmyelinated ganglion cells had increased The radially and spirally running unmyelinated fibres inside the organ of Corti remained intact as long as the inner hair cells and supporting cells were preserved Both efferent and afferent tunnel-crossing fibres appeared to undergo degeneration when all the sensory cells had degenerated

The secondary degeneration of first order neurons, following damage to the organ of Corti seemed to be a delayed phenomenon its full development not apparent until at least 4 weeks after the cessation of treatment.

Applying the place theory of hearing sensitivity thresholds at each frequency were related to the extent of hair cell loss at specific distances along the basilar membrane In this correlation it was found that all animals which displayed a deterioration of hearing also had significant disturbance in their hair cell pattern When groups of animals with similar hearing losses were pooled together a still better correlation between hearing losses and sensory cell destruction was achieved than in individual animals. Thus a slight hearing loss was related to a moderate loss of OHCs and a more severe impairment to hearing was associated with a severe degeneration of cochlear hair cells. Hence the absence of the first row of OHCs was related to a hearing loss of 18 dB when two inner rows of the OHCs were missing hearing had deteriorated by 38 dB and when all the OHCs had degenerated but the IHCs were still essentially intact the accompanying hearing loss was 42 dB When in addition to a complete loss of OHCs, more than 10% of the IHCs had degenerated hearing loss was correspondingly more severe and when nearly all the cochlear hair cells were absent, hearing loss was about 80 dB

In some of the animals, however a moderate degeneration of the OHCs was not accompanied by a corresponding change in hearing threshold

In the cochleas of 12 animals relatively abrupt shifts in hearing threshold were recorded and subsequent histological examination of these cochleas revealed corresponding restricted areas of hair cell damage. In these 12 animals it was possible to analyse the spatial arrangement of frequency localisation along the basilar membrane These results correlate rather well with results from earlier studies done with other methods.

ZUSAMMENFASSUNG

Vergleichende Untersuchungen über die degenerativen Veränderungen in den cochlearen Haarzellen wurden an 94 Meerschweinchen nach Verabreichung von Gentamycin, Kanamycin und Neomycin in verschiedener Dosierung und Zeitdauer durchgeführt. Nach einer Überlebensdauer von 0 Tagen bis 10 Monaten wurden die Tiere dekapitiert und die pathologischen Veränderungen im Schläfenbein licht und elektronenmikroskopisch untersucht. Vollständige Cochleogramme wurden für die 68 Meerschweinchen angefertigt, welche zu der Dekapitation überlebt hatten.

Die frühesten ultrastrukturellen Degenerationszeichen wurden, unabhängig von dem verabreichten Antibiotikum, in den ausseren Haarzellen der Basalwindung beobachtet. Neben Veranderungen an den lateralen Doppelmembranen kam es zum Auftreten von dunklen Einschlusskorpern im subcuticularen Cytoplasma dieser Zellen. In spateren Stadien kam es zu einer Erweiterung der Zwischenraume zwischen den abgeflachten Membranen, mit nachfolgender Vakuolisierung der lateralen Zellabschnitte und schliesslich, unter Ruptur der Plasmamembran und A stritt der Zellorganellen in den Noel'schen Raum zu einer volligen Desintegration der Zellen. In einem frühen Stadium der Degeneration wurden Anschwellungen, vermutlich geschwollene afferente Nervenendigungen und Dendriten, unterhalb der inneren Haarzellen beobachtet.

Das durch die drei Antibiotika hervorgerufene Schadensmuster ist unterschiedlich. Neomycin schien zuerst die Hakenregion und die Spitzenwindung anzugreifen, während Gentamycin und Kanamycin gewöhnlich zuerst die inneren Haarzellen in der oberen Basalwindung und im Hakengebiet gleichzeitig zerstörte. Neomycin liess auch deutlich eine schädigende Affinität zu den inneren Haarzellen der Spitze erkennen, welche nach Verabreichung von Gentamycin und Kanamycin selten geschädigt waren. Das Ausmass der Schädigung, welche die äusseren Haarzellen betraf, war im allgemeinen ausgedehnter. Das Gebiet in der Cochlea zwischen einer nahezu normalen Population von äusseren Haarzellen und einem vollständigen Ausfall dieser Zellen war gewöhnlich breiter nach Kanamycin als nach Gentamycinbehandlung.

Unsere Ergebnisse zeigen, dass bezüglich der Wirkung von ototoxischen Antibiotika grosse Variationen bei einzelnen Tieren bestehen. Der Grad der schädigenden Wirkung solcher Substanzen auf das Cortische Organ kann deshalb nicht quantitativ in Dosiseinheiten ausgedrückt, sondern sollte durch die Untersuchung der Haarzellenpopulation eines jeden einzelnen Tieres bewertet werden. Ferner sollten wegen des Verzögerungseffektes der basischen Aminoglykosid-Antibiotika die Versuchstiere mindestens drei Wochen nach Abschluss der Behandlung überleben, um entsprechende Untersuchungen über den Zusammenhang von funktionellen und morphologischen Veränderungen durchgeführt werden.

Zur Untersuchung der Beziehung zwischen einer Schädigung von sensorischen Zellen und von Neuronen in der Cochlea wurden die neuronalen Elemente in ausgewählten Cochleasegmenten, die eine Haarzellenschädigung aufwiesen, untersucht.

Ein partieller oder totaler Verlust nur von äusseren Haarzellen in einem bestimmten Cochleasegment, war mit keiner entsprechenden Rarefizierung oder Verlust von Neuronen verbunden. Wenn die inneren Haarzellen degeneriert waren, dann war auch die Zahl der Neuronen im Spiralganglion und Lamina spiralis ossea deutlich vermindert, vorausgesetzt die Überlebenszeit war lange genug, dass die Degeneration ihren Verlauf nehmen konnte. Im letzteren Fall überlebten 10–25 % der Fasern in der Lamina spiralis ossea und ungefähr 40 % der Zellen im Ganglion spirale. Die Mehrheit dieser erhaltenen Neuronen erschien elektronenmikroskopisch normal, obgleich die relative Anzahl von myelinfreien Ganglienzellen erhöht war. Die radiär und spiralenförmig verlaufenden myelinfreien Fasern im Inneren des Corti-Organs verblieben intakt, solange die inneren Haarzellen und Stützzellen erhalten waren. Sowohl efferente als auch afferente Tunnelbrückenfasern schienen der Degeneration anheimzufallen, wenn alle sensorischen Zellen degeneriert waren.

Die sekundäre Degeneration von Neuronen erster Ordnung im Anschluss an eine Schädigung des Corti-Organs scheint ein verzögerter Vorgang zu sein, dessen vollständige Entfaltung nicht vor Ablauf von mindestens 4 Wochen nach Absetzen der Behandlung manifest wurde.

Zur Untersuchung der Beziehungen zwischen cochlearer Haarzellenschädigung und Hörempfindlichkeit sowie der r systematischen Ermittlung der Frequenzlokalisation in der Cochlea wurden 42 Meerschweinchen zuerst unter die Bedingungen einer Reflexhörprüfung nach der Methode von Anderson und Wedenberg (1965) gebracht und nach einmaliger Gehörausschaltung weiteren Gehörprüfungen unterzogen. Eine cochleare Schädigung wurde durch tägliche subcutane Injektion von Gentamycin, Kanamycin oder Neomycin in toxischen Dosen gesetzt.

Nach Abschluss der Behandlung und Erreichen einer stabilen *Hörschwelle* wurden die Tiere dekapitiert und die pathologischen Veränderungen am Schläfenbein untersucht.

Entsprechend der Ortstheorie des Hörens wurden die Empfindlichkeitsschwellen in jedem Frequenzbereich zum Ausmass des Haarzellenverlustes in bestimmten Abständen an der Basilarmembran in Beziehung gesetzt. Dabei wurde gefunden, dass alle Tiere mit einer Hörverminderung auch eine signifikante Störung ihres Haarzellenmusters aufwiesen. Daraus ergab sich bei leichter Hörverminderung ein geringer Verlust von äusseren Haarzellen, während ein schwerer Hörschaden mit einer starken Degeneration der cochlearen Haarzellen verbunden war. Der Ausfall der ersten Reihe von äusseren Haarzellen bedingte einen Hörverlust von 18 dB, der Ausfall von zwei inneren Reihen von äusseren Haarzellen resultierte in einem Hörverlust von 38 dB. Die Degeneration aller äusseren Haarzellen führte bei weitgehender Intaktheit der inneren Haarzellen zu einem Hörverlust von 42 dB. Waren zusätzlich zu einem vollständigen Verlust der *äusseren Haarzellen mehr als 10 %* der inneren Haarzellen degeneriert, dann war der Hörverlust entsprechend schwerer und betrug bei Ausfall nahezu aller cochlearen Haarzellen etwa 80 dB. Bei einigen Tieren war jedoch eine geringe Degeneration der äusseren Haarzellen nicht von einer entsprechenden Hörschwellenveränderung begleitet.

In der Cochlea von *12* Tieren wurden verhältnismässig abrupte Veränderungen der Hörschwelle beobachtet. Die nachfolgende histologische Untersuchung deckte korrespondierende, unterscheidbare Areale einer Haarzellenschädigung auf. Bei diesen 12 Tieren konnte die räumliche Anordnung der Frequenzlokalisation an der Basilarmembran analysiert werden.

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A Clinical Study

BY

EINO KOKKO

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CONTENTS

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1 INTRODUCTION AND PURPOSE OF THE STUDY

Thanks to antibiotics and chemotherapeutics, the prognosis of acute otitis media has improved considerably. Many of the complications which used to be common have become rare, and even when they occur they are seldom fatal. The improved therapeutic facilities for acute otitis media have been accompanied by a continuous fall in the incidence of chronic otitis media. This development has been favourable above all in districts where distances are not inconveniently long and where treatment at specialist level has been adequately available. The effectiveness of antibiotics and chemotherapeutics in acute otitis media is indisputable, but many find that excessive confidence in drug therapy as a universal panacea, and the omission of paracentesis in the treatment of acute otitis media, are the worst culprits in the development of a new middle ear problem chronic secretory otitis media, and its high incidence in the last twenty years.

Politzer (1867) described the clinical picture of chronic secretory otitis media but in spite of this the condition has not been too well known among otologists even up to the last few years. The accumulation of glue-like secretion in the tympanum, which is typical of chronic secretory otitis media, may have passed unnoticed owing to the slightness of the symptoms. Furthermore, the resistance of the disease to therapy has produced poor therapeutic results. The etiology of the disease has been unclear and due to the wide variety of therapeutic principles and the large number of therapeutic methods used, it has been difficult to make a comparison of the results. Not until Armstrong (1954) published his report on the use of a tympanostomy tube in the treatment of chronic secretory otitis media did the situation become considerably clearer and with this method the therapeutic results have improved. The experimental, histological histochemical and immunological studies of the last two decades have also thrown light on the etiology of the disease and created better conditions for successful treatment.

A number of sufficiently precise studies, with adequate follow up periods have been reported in recent years concerning the effectiveness and complications of tympanostomy tube therapy (Mawson & Fagan, 1971 Kilby et al. 1972, Hussl, 1973b) However the follow-up periods are so far still relatively short.

The purpose of the present study was to investigate on the basis of clinical material,

- the clinical picture of chronic secretory otitis media, giving particular attention to the age at the onset of symptoms, to other concomitant diseases influencing the outbreak of the secretory otitis media, to the bacteriology of the middle ear effusion, and the possible complications of the disease,
- the required duration of tympanostomy tube therapy in chronic secretory otitis media, and the most frequent complications of this therapy
- the hearing loss in chronic secretory otitis media, the improvement of hearing produced by tube therapy and the permanence of the improvement achieved.

2 REVIEW OF THE LITERATURE

2.1 CLINICAL PICTURE OF CHRONIC *SECRETORY OTITIS MEDIA*

Politzer (1867) was the first to describe the clinical picture of secretory otitis media, but even before his time there were in the literature reports on ear diseases which evidently referred to sectory otitis media (Wathen 1756 Cooper *1801)*

The most essential characteristic of secretory otitis media is middle ear effusion without the symptoms of infection accompanying acute otitis media. Acute secretory otitis media according to Tiedemann (1966) is a sequel to rhinopharyngitis and usually requires no particular therapy whereas chronic secretory otitis media according to Zöllner (1942) refers to those cases that have escaped early diagnosis and are of long duration

Senturia (1970) divided the middle ear effusions into serous seropurulent purulent mucopurulent and mucous According to him the protein content in the serous type was 11 4 g% in the purulent 7 7 g% and in the mucous 5 1 g% Usually the effusions in chronic secretory otitis media are divided into mucous and serous. According to Irstamm (1954) the effusion in children is usually mucous and viscous Sadé (1965) assumed that the serous effusion is derived from PAS negative and the mucous effusion from PAS-positive glands Palva et al. (1974b) studied the protein content of the mucous effusion in children s chronic secretory otitis media. In their material of 69 samples the mean protein content was 9 9 g% against 7 1 g% in the serum

Leegaard (1923) studied the causes of impaired hearing in school children and found that "Eustachian catarrh" was the cause in 24 7 % In a corresponding study by Lumio (1957) the share of chronic secretory otitis media was 51 % and in the material published by Jusélius (1958) 57 %

Chronic secretory otitis media is most common in children under 10 years of age and *in most materials expressly in the 4—8-year* olds (Hoople 1950 Armstrong 1957 Lenoe, 1962 Kersley & Wickham 1966 Draper 1967 Hussl 1973b) In Hussl s opinion the disease also occurs in younger children but is diagnosed less often since symptoms are slight. According to Watson (1969) impaired hearing in children was due to chronic secretory otitis media in 81 % of the 5-year olds but in 0 % of the 13-year *olds On the basis of serial sections and direct* middle ear measurements Holborow (1970) advanced the opinion that the opening mechanism of the Eustachian tube is not properly developed at birth and that the interval from birth to the 7th year of age is most critical period in view of the relative tubal insufficiency

In many materials chronic secretory otitis media is more common among boys than girls. Draper s (1967) series contained 61.2 % boys *and 38 8 % girls. The distribution was much the* same in the series reported by Eagle (1946), Stevens (1958) and Solow (1958) According to Solow this accords with the incidence of respiratory allergy among both sexes before puberty

In chronic secretory otitis media the appearance of the drum varies greatly Malcomson (1969) divided the drums into 18 groups on the basis of their appearance. Reduced mobility of the drum, when tested with Siegle s pneumatic speculum is considered one of the most reliable diagnostic signs (Davison 1958 Hussl 1973a) The final diagnosis can often not be *made even with a microscope and*

paracentesis may be the only means of verifying it (Hussl, 1973a)

The mean impairment of hearing in chronic secretory otitis media ranges in the different materials from 25 dB to 45 dB (Silverstein et al. 1966 Cohen & Sadé 1972, Kilby et al. 1972; Mawson & Fagan, 1972, Hussl 1973b) In the series of Cohen & Sadé and Mawson & Fagan the impairments followed Gauss's curve.

According to Dawes (1970) chronic secretory otitis media seldom leads to the development of adhesive otitis media. This agrees with the finding by Ojala (1953) that the development of chronic adhesive otitis media is preceded by recurrent infections exceeding a given minimum. According to Dawes, the most common conditions following chronic secretory otitis media include atrophy of the drum necrosis of the long process of the incus, disappearance of the superstructure of the stapes, and tympanosclerosis. Zalin (1963) claimed that chronic secretory otitis media is an intermediate phase in the development of cholesteatoma. In a material of 396 children who had had chronic secretory otitis media Zalin found pre-epidermosis at follow up examination in 17 % against an incidence of 3 % in the normal population. Jordan (1963) repord 11 cases in which cholesteatoma of the attic developed during the course of treatment for chronic secretory otitis media.

2.2. ETIOLOGY AND PATHOGENESIS

The etiology of secretory otitis media has long been unclear as evidenced also by the large number of synonyms used. serous otitis media, secretory otitis media, adhesive otitis media, otosalpingitis, tubotympanitis, hydrotympanum and glue ear although the disease is always the same.

There are two theories of the pathogenesis of secretory otitis media. the hydrops ex vacuo theory and the infection theory The hydrops ex vacuo theory which was the first to be evolved, was presented by Politzer (1867) and supported by his contemporaries Zaufal (1870) and Bezold (1883) According to this theory the cause of secretory otitis media is the hermetic closing of the Eustachian tube which results in the diffusion of middle ear gases into the blood vessels. The negative pressure then resulting in the middle ear produces a transudation of serum from the vessels into the tympanum. Such transudation has been found in connection with barotrauma but, according to van Dishoeck (1948) transudation presupposes a negative pressure of 150 cm H_2O while the maximum negative pressure measured in the middle ear has been 50—60 H_2O On the other hand, Flisberg et al. (1963) showed that a negative pressure of 20—30 mm Hg in the middle ear produced a bright yellow thin effusion in 15 minutes. In many animal experiments (Holmgren, 1940 Proud & Odoi, 1970 Paparella et al., 1970) this could be verified. Tönder & Gundersen (1971) also found support for the hydrops ex vacuo theory from their protein analyses of the middle ear effusion.

Brieger (1914) found that the Eustachian tube is hardly ever completely blocked in secretory otitis media and that the hydrops ex vacuo theory could not adequately account for the development of a middle ear effusion. In his opinion, the effusion was an exudate and was produced by an inflammatory process in the middle ear mucosa. This infection theory was supported by Kümmel (1914) Neuman (1930) Schlander (1932) Siirala & Lahikainen (1952) and Vuori (1959) Senturia, on the basis of numerous animal experiments, also came to the conclusion that secretory otitis media is of infection origin (Senturia et al. 1958, 1960 Senturia, 1963 1970) In accordance with the infection theory the effusion in chronic secretory otitis media in many otologists opinion is bacterial (Forschner 1925 Biegvad, 1931 Senturia et al. 1958 Silverstein et al. 1966; Bernstein & Hayes, 1971) whereas the supporters of the hydrops ex vacuo theory claim that the effusion is sterile (Scheibe 1892, Jordan, 1949 Ivstamm 1954 Tönder & Gundersen, 1971) Of the 50 samples reported on by Bernstein & Hayes (1971) 60 % were sterile. The most common bacteria were *Hemophilus influenzae* *Streptococcus* and

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Chronic secretory otitis media is most common in children under 10 years of age and in most materials expressly in the 4—8-year olds (Hoople 1950· Armstrong 1957 Lemon 1962, Kersley & Wickham 1966 Draper 1967 Hussl 1973b) In Hussl's opinion the disease also occurs in younger children but is diagnosed less often since symptoms are slight. According to Watson (1969) impaired hearing in children was due to chronic secretory otitis media in 81 % of the 5-year olds but in 0 % of the 13-year olds On the basis of serial sections and direct middle ear measurements Holborow (1970) advanced the opinion that the opening mechanism of the Eustachian tube is not properly developed at birth and that the interval from birth to the 7th year of age is most critical period in view of the relative tubal insufficiency

In many materials chronic secretory otitis media is more common among boys than girls Draper s (1967) series contained 61 2 % boys and 38 8 % girls. The distribution was much the same in the series reported by Eagle (1946) Stevens (1958) and Solow (1958) According to Solow this accords with the incidence of respiratory allergy among both sexes before puberty

In chronic secretory otitis media the appearance of the drum varies greatly Malcomson (1969) divided the drums into 18 groups on the basis of their appearance. Reduced mobility of the drum when tested with Siegle s pneumatic speculum is considered one of the most reliable diagnostic signs (Davison 1958 Hussl 1973a) The final diagnosis can often not be made even with a microscope and

carried no mucus-secreting elements. According to them serous effusion is transudate, and a result of increased capillary permeability

On the basis of protein and enzyme analyses of the middle ear effusions, Paiva et al. (1974a, 1974b) claim that the middle ear effusion cannot be transudate but it must be a result of active secretion. In their studies, the middle ear effusion showed considerably higher levels of lactate and malate dehydrogenase, acid phosphatase, aspartate aminotransferase and alanine aminotransferase than the serum. On the other hand the alkaline phosphatase levels were equally high in the serum and middle ear effusion, while the nonspecific esterase level in the serum was higher than the middle ear effusion.

Most otologists are agreed that adenoids sinusitis, nasopharyngeal infections and cicatricial changes of the tubal orifice play a part in the etiology of chronic secretory otitis media.

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The role of allergy in the etiology of chronic secretory otitis media has been variously described. According to Dohlman (1943) allergy was the cause in a number of cases. Jordan (1949) attributed the disease to allergy in 74 % and in a later material (1952) in no less than 67 % of the cases. Lecks (1961) quoted equally high percentages. According to Draper (1967) allergic children had an incidence of secretory otitis media twice that of non-allergic children. In the other materials published, the share of allergy has been considerably lower (Hotchkiss, 1948 Suehs, 1952· Stevens, 1958, Lemon, 1962 Silverstein et al., 1966; Kersley & Wickham, 1966) Wright & Kapadia (1969) failed to find eosinophils in the middle ear effusion of any of the patients in their material.

Cleft palate patients have been found to have a remarkably high incidence of chronic secretory otitis media. It has long been known that impaired hearing is very common among the cleft palate patients (Sataloff & Fraser 1952, Holmes & Reed 1955 Halfond & Ballenger 1956, Skolnik, 1958 Masters et al., 1960· Holborow 1962, Graham & Lierle, 1962, Aschan 1966) but Stool & Randall (1967) were the first to show that it was mainly due to chronic secretory otitis media. In materials published later nearly 100 % of the cleft palate cases have had chronic secretory otitis media (Paradise & Bluestone, 1969· Paradise et al 1969) According to Holborow (1970) the cause of secretory otitis in cleft palate patients is the impaired function of the musculus tensor veli palatini and the resulting dysfunction of the Eustachian tube

Other causes of chronic secretory otitis media have also been suggested. Hopp et al. (1964) gave immunization as a possible cause· in their experiments with guinea pigs immunized with bovine serum albumin they managed to bring about a clinical picture reminiscent of secretory otitis media. Davison (1958) also listed systemic factors such as obesity and hypothyroidism among the possible causes.

Many otologists are of the opinion that the incidence of chronic secretory otitis media has increased considerably during the era of antibiotics, and attribute this to an inadequate administration of the antibiotics and the omission of paracentesis in the treatment of acute otitis media (Suehs, 1956· Armstrong 1957 Davison, 1958, Friedmann, 1963 Paiva et al. 1974a, 1974b)

2.3 TREATMENT AND ITS RESULTS

Most otologists have observed the ineffectiveness of paracentesis and myringotomy in the treatment of chronic secretory otitis media, although Senturia et al. (1960) were of the opinion that weekly paracentesis under general anaesthesia sufficed in most cases. Attempts to improve the effectiveness of paracentesis have been made by making several incisions (Lemon 1962, Kersley & Wickham, 1966) or by combining it with retrograde tubal inflation, but the latter has been reported to have produced lethal complications (Åhren & Thulin, 1965

Pneumococcus. Bacteriological sterility has also been attributed to viral etiology Berglund et al (1966) managed to isolate RS viruses from the middle ear effusion in acute otitis media Siirala (1957) attributed bacteriological sterility to the bactericidal and bacteriostatic effect of the middle ear effusion which he had previously verified in acute otitis media (Siirala & Lahikainen 1952) It has been proved later that this effect is derived from the IgA secreted by the mucous glands (Bernstein et al 1973)

While most authors are of the opinion that complete blockage of the Eustachian tube in secretory otitis media has not been demonstrated, they are unanimous that there must be a relative dysfunction of the Eustachian tube Sato (1939) showed with animal experiments that the normal ciliary movement quickly removed foreign particles from the tympanum The same result was reported by Compere (1958) who examined the tubal function with water soluble contrast medium When the tubal function was normal the contrast medium introduced into the tympanum through the eardrum disappeared in a matter of minutes, whereas in chronic secretory otitis media there were a few cases when the tympanum was never cleared although tubal inflation was relatively easy A similar result was reported by Rogers et al (1962) who studied the tubal function in dry and moist perforated ears with fluorescence techniques Westergaard (1970) examined the tubal function tympanometrically with Flisberg s aspiration techniques. None of 18 children with chronic secretory otitis media all with tympanostomy tubes in position was able to reduce negative pressures in any phase of the treatment whereas immediately after insertion of the tubes, 54 % of the patients and after 6 months of treatment 76 % could reduce positive pressures. A similar finding was reported by Silverstein et al (1966)

Sadé (1965 1966a 1966b 1967 Sadé & Weinberg 1969) has extensively described the histology of the mucosa of the normal middle ear and of one affected with secretory otitis media According to Sadé the mucosa of the healthy middle ear at the orifice of the tube is pseudostratified columnar and ciliated, and further back in the tympanum it has a columnar cuboidal or flat-cell structure He reports that ciliated epithelium extends in the normal middle ear from the tubal orifice over c. one-third to two-thirds of the tympanal mucosa but normally not to the antrum to mastoid air cells and the medial surface of the eardrum According to Sadé the rate of ciliary movement in dry perforated ears is 1—1.5 mm/sec whereas in moist perforated ears the movement is slower or none Secreting elements are situated in areas with ciliated epithelium and according to Sadé secretory otitis media involves either a hypersecretion of mucus or an impairment of ciliary function Lim & Hussl (1969) found ciliated epithelium also in the antrum mastoid air cells and the medial surface of the eardrum They reported two types of secreting cells on the mucosa of the healthy middle ear goblet cells and intermediate cells. Lim et al (1973) found with electron microscopy that the distribution of mucus-secreting cells was the same as that of ciliated cells.

Friedmann (1963) found that in guinea pigs, infection produced a heavy increase in the goblet cells and glandular elements of the columnar epithelium within a fortnight Friedmann attributed the chronicity of secretory otitis media to the accumulation of mucus caused by the mucosal changes regardless of whether the tube was patent or not

Tos & Bak Pedersen (1972 1973 Bak Pedersen & Tos, 1971 1973) studied the incidence of glands on the middle ear mucosa in different pathological conditions They reported that the density of mucous glands on the middle ear mucosa in secretory otitis media was 7 1/mm² in chronic otitis media 3 4/mm² in otosclerosis 1 7/mm² and in tympanosclerosis 0 6/mm² Furthermore in secretory otitis media 90 % of the glands were active against only 0—20 % in the rest of the above diseases

In their electron microscope studies Lim & Birck (1971) found a high rate of mucus secreting elements from mucosal biopsies taken from middle ears with mucous secretion whereas in serous otitis media the mucosa

carried no mucus-secreting elements. According to them, serous effusion is transudate and a result of increased capillary permeability

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Fairman et al 1968) Tubal catheterization and Valsalva s manoeuvre were earlier in general use but Hussl (1973b) pointed out that they alone did not lead to the desired result.

Adenotomy and treatment of the nasal and nasopharyngeal infections cure a large propor tion of the chronic secretory otitis media according to Lemon (1962) and Gottschalk (1972) *whereas Mawson & Fagan (1972) find* that "adenoidectomy as a primary form of treatment has no justification

Many others methods of treatment were formerly used for chronic secretory otitis media such as nasopharyngeal irradiation (Adams 1956 Suehs 1956 Aschan & Nohrmann 1957) destruction of lymphatic tissue at the tubal orifice with trichloracetic acid brushing (Ivstamm 1954) removal of hyperplastic tonsils (Malcomson 1969) antiallergic therapy (Jor dan 1949) systemic (Oppenheimer 1968) or local (Torrey 1971) steroid therapy alpha chymotrypsin treatment to reduce the viscosity of the effusion (Kersley & Wickham 1966) irradiation of the Eustachian tube (Beck, 1969) exhairesis of the Jakobson nerve (Malcomson 1969) *tympanotomy to remove the tenacious* effusion (Mawson & Brennand 1969) Mas toidectomy has been recommended for the treatment of cases resistant to therapy (Davison 1958 Stevens, 1962 Grahne 1964)

According to Politzer (1878) persistent perforation was considered desirable already in the 17th century in the treatment of ear diseases without any definite indications but Himly and Cooper (1801) were the first to try permanent perforations in the therapeutic sense

Politzer himself treated secretory otitis media with excision of a part of the drum sphirotomy incisions and lapis coagulation of wound edges corrosion of perforations with sulphuric acid and galvanocautery but *failed to obtain permanent* results. He tried to keep the perforations open by *inserting a small rubber tube*, but the tubes were too quickly extruded just as were the silver cannulas of Bonnafont and the aluminium tubes of Voltolini *two of his contemporaries*. Hotchkiss (1948) tried to produce persistent perforations by a corneal trephine but his results were also *unsatisfactory* Armstrong (1954) was the first who managed to ventilate the tympanum for several months by means of vinyl tubes. In recent years the tympanostomy tubes have gained extensive popularity in the *treatment of chronic secretory* otitis media, several tube types have been designed and many materials have been used (Lindeman & Silverstein 1964 Schmidt & Bolhuis, 1965 Silverstein 1965 Feuerstein 1966 Turner 1967 Wilson 1969)

Until the last few years the therapeutic results have been difficult to compare since the therapeutic indications and methods have been extremely varied and the follow up period in many materials have been inadequate.

Stevens (1962) invited 53 children, whom he had treated for "serous otitis media" 5—7 years *previously to come for a follow up examination*. 32 children attended the examination. Drum changes were seen in 79 % of the ears, and in 33 % the changes were of a severe degree Three *ears had an adhesive drum and one a* posterosuperior perforation and cholesteatoma. Five ears were still affected with serous otitis media" On the whole the changes were more severe in the ears in which the effusion had originally been thicker

Gottschalk (1972) reported good results with *the conservative treatment of a material of 182* patients (258 ears) On admission the patients were first subjected to a meticulous adenoidectomy reaching to the fascia, and at the same time two myringotomy orifices were made to remove the effusion as completely as possible. There was an immediate relapse in only 8 ears. Within 12 months the disease had not recurred in 68 % of the re-examined ears (200 ears) Paracentesis had been made in only 2 ears after the institution of therapy all others had healed with drugs In *Gottschalk s opinion when the disease recurred* weeks or months later this was not a therapeutic failure but a new onset of the disease This view explains the good results reported.

In recent years several reports have been published on the results of tympanotomy tube therapy Neveling (1968) reported good hearing results in all subjects of his material of 84

12 9 % later in the course of the tube treatment. All infections healed without complications In only one drum was a perforation left after extrusion of the tube The tympanostomy tube had to be inserted twice in 20 2 % and three or more times in 3 2 % Preoperatively the hearing level within the speech frequencies in the total material was 40 dB (mean of 500 1000 and 2000 Hz) and immediately after tube insertion 10 dB 114 ears were re-examined 6—24 months after the insertion 45 6 % of the drums were normal 26.3 % showed retraction of pars tensa 11 4 % had tympanosclerosis and 10 4 % atrophic scars or an atrophic posterosuperior quadrant. One drum was found to have a persistent perforation and one ear developed mastoiditis nigra which was treated with mastoidectomy and tympanotomy No instance of complete adhesive otitis media was noted but one of the drums adhered to the head of the stapes. No cholesteatoma was found at the follow up examination In 5 ears the tube was in position at this examination

In the materials described above drum changes following the tympanostomy tube therapy were common and increased as a function of the duration of the therapy (Mawson & Fagan 1972 Kilby et al 1972, Hussl 1973b) In the material of Mawson & Fagan, 40 % of the drums and Hussl s material 45.6 % were normal at the follow up examination 6—60 months after the insertion of the tube. The most common changes were tympanosclerosis and retraction of the drum According to Mawson & Fagan drum changes are not necessarily combined with impaired hearing Both materials contained only one persistent perforation each. Mawson & Fagan s material contained one posterosuperior perforation and cholesteatoma, but there was no instance of attic cholesteatoma in either material although Jordan (1963) reported 11 cases in connection with the treatment of chronic secretory otitis media. The recurrence rate in Mawson & Fagan s material was 10 % much the same as the rates quoted by Lemon (1962) Schuknecht et al. (1964), Schmidt & Bolhuis (1965) and Feuerstein (1966) The hearing results in the above materials were very different. The results, almost 100 % good reported by Neveling (1968) and Tarab (1969) apparently referred to the time immediately after insertion of the tube and are therefore not comparable as such with the late results In the late results reported by Mawson & Fagan the hearing level in 65 % of the ears was better than 20 dB and in 9 % poorer than 30 dB.

3 MATERIAL

The material comprised all patients under 15 years of age treated in 1965—71 for chronic secretory otitis media in the wards of the Department of Otolaryngology of Oulu University a total of 181 children (Table I) All these patients had undergone repeatedly paracentesis which had yielded glue-like secretion. In 142 patients the affection was bilateral, in 39 unilateral, and the total number of ears treated was 323 (Table II) There were 106 boys (59 %) and 75 girls (41 %)

164 patients were treated by inserting a tympanostomy tube into 290 ears, and 17 patients, total 33 ears, by repeated paracentesis (Table II) The number of the cases treated had increased continuously year by year In 1965—66 only 2 children were treated in the wards for chronic secretory otitis media, but by 1971 the figure had risen to 53 children (Table I)

The material came from a district which, in 1965 covered an area of 130 000 km and had 550,000 inhabitants, and where the longest distances to the hospital were c. 500 km. In 1971 after the construction of new hospitals, the area of the hospital district was 30,000 km with 260,000 inhabitants, and the maximum distance to the hospital was c. 250 km.

The majority of the patients had, before admission, been treated by general practitioners, and the treatment had consisted of repeated paracentesis and courses of antibiotics.

Table I. *The number of fresh cases treated annually*

Year	No. of patients
1965	1
1966	1
1967	22
1968	21
1969	40
1970	43
1971	53
Total	181

On their first admission to the hospital, the patients underwent a normal otological examination which additionally included a myringotomy and the aspiration of a sample for bacterial culture, radiography of the ear and sinuses, and an audiometric hearing test. Where necessary the part possibly played by allergy was also investigated. Tympanostomy tubes were inserted as a primary treatment in a small number of patients. In most cases, however the patient first underwent adenotomy and was then seen weekly or fortnightly tubes being inserted later if the disease did not heal. A number of patients only underwent adenotomy or adenotonsillectomy without tympanostomy tubes.

Table II. *Distribution of the series by mode of treatment and sex*

Mode of treatment	No. of patients							Total no. of ears
	female	(%)	male	(%)	unilat.	bilat.	total	
Tympanostomy	68	(41)	96	(59)	38	126	164	290
No tympanostomy	7	(41)	10	(59)	1	16	17	33
Total	75	(41)	106	(59)	39	142	181	323

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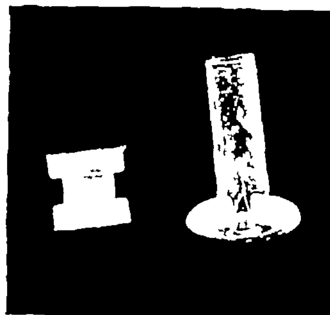


Fig 1 The models of tympanostomy tube used. Right, a self made tube of polyethylene (PE 100) and left the silastic tube (Donaldson)

Tubes were inserted under general anaesthesia by young resident surgeons. In most cases *self made polyethylene (PE 100) tubes* and in a smaller group commercial silicone tubes, were used Before the insertion the external meatus was cleaned mechanically only The paracentesis was usually made in the anteroinferior quadrant of the drum but if this was technically difficult in the posteroinferior quadrant. In some cases of long duration in which the inferior part of the drum was atrophic, the tube was placed in the anterosuperior quadrant within the normal drum area. After the effusion had been aspirated, the tube was placed in the para centesis aperture with very small straight alligator forceps, under microscopic control With some experience the prosedure lasted only a few minutes.

Subsequently the patient was usually given a 7 day course of antibiotics. He then visited the outpatient clinic first at monthly intervals and later at intervals of 2—3 months Possible crusts around the tube were removed, their openness was assured and an audiometric hearing test carried out If chronic secretory otitis media recurred after the extrusion of the tube, another tube was inserted

The tubed patients or their parents were instructed not to let water get into the tubed ears. The patients were allowed to take a bath in a bath tub or sauna and to swim if they put cotton wool moistened in paraffin into the external meatus but they were not allowed to dive All respiratory infections were treated carefully The patients parents were requested to get in touch with the treating physician immediately if there was any discharge. The discharge was removed by syringing the ear with physiological saline ear drops were used locally and antibiotics orally

Data on the patients medical history on their period of hospitalization and outpatient clinic visits were obtained from case histories, and complemented if necessary in connection with the follow up examination This was carried out during the autumn of 1972, all the 181 patients of the material being invited with an attendance of 166 (91 6 %) On this occasion the present author personally carried out the otological examination of all patients using the operating microscope to help in ascertaining the drum status. At the same time an audiometric hearing test for air and bone conduction was carried out on all patients over 4 years of age Due to poor cooperation the hearing results of a number of the youngest patients were unreliable and had to be excluded from the statistical analyses. The audiometric test was carried out by the two trained examiners who had made the earlier audiometric tests. All hearing level examinations were made with the Madsen Model OB 60 audiometer calibrated according to the ISO standards The results were analysed at the Oulu University Computer Centre Student s t test was used for the statistical comparison of the results

4 RESULTS

4.1 CLINICAL DATA

4.1.1 The tympanostomy group

The chronic secretory otitis media of 164 children, 96 boys (59 %) and 68 girls (41 %) was treated by inserting tympanostomy tubes into a total of 290 ears. In 126 children 73 boys (58 %) and 53 girls (42 %) the disease was bilateral, and in 38 children, 23 boys (61 %) and 15 girls (39 %) it was unilateral (Table II)

4.1.1.1 Preoperative history and data from the time of treatment

In the 38 children with unilateral disease the other ear was healthy in 30 cases. In 2 patients the contralateral ear had been treated with mastoidectomy for chronic suppurative otitis media, in 2 ears a cholesteatoma and in 2 a dry drum perforation had been diagnosed, and another 2 ears were affected with chronic secretory otitis media which healed with paracenteses.

Half of the patients had, or had previously had, other diseases (Table III) Congenital cleft palates were operated on, at the latest in connection with the tube treatment. Two of the 5 mentally retarded children apparently were congenitally deaf. Perceptive hearing defects, of unknown etiology were bilateral.

One patient with bilateral chronic secretory otitis media had become deaf in one ear following paracentesis carried out by a general practitioner

104 children had previously had suppurative otitis media, while 60 children had no previous ear history Purulent discharge from the ear had occurred in 30 children.

The onset of the symptoms of secretory otitis media had usually occurred before school age (Table IV) The biggest age group consisted of

Table III. *Other diseases of the tympanostomy patients*

Diagnosis	No. of patients
Sinusitis	24
Recurrent respiratory tract infections	19
Palatoschisis	10
Abnormal status of nasopharynx	6
Chronic tonsillitis	5
Mental retardation	5
Allergic rhinitis	4
Perceptive hearing loss	2
Premature birth	2
Concealed cleft palate	1
Schizophrenia	1
Operated oesophageal atresia	1
Treated facial paresis	1
Atrial septal defect	1
Ventricular septal defect	1
Bronchial asthma	1
Ozaena	1
History of otogenous meningitis	1
Anaemia	1
Total	87

Table IV *Age at onset of the symptoms of secretory otitis media in the tympanostomy group*

Age, years	No. of patients
0— 1	31
1— 2	17
2— 3	5
3— 4	12
4— 5	11
5— 6	13
6— 7	9
7— 8	24
8— 9	11
9—10	9
10—11	5
11—12	6
12—13	4
13—14	4
14—15	3
Total	164

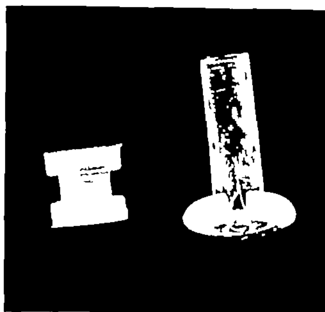


Fig 1 The models of tympanostomy tube used. Right, a self made tube of polyethylene (PE 100) and left, the silastic tube (Donaldson)

Tubes were inserted under general anaesthesia by young resident surgeons In most cases self made polyethylene (PE 100) tubes and in a smaller group commercial silicone tubes were used Before the insertion the external meatus was cleaned mechanically only The paracentesis was usually made in the anteroinferior quadrant of the drum but if this was technically difficult, in the posteroinferior quadrant In some cases of long duration in which the inferior part of the drum was atrophic the tube was placed in the anterosuperior quadrant within the normal drum area. After the effusion had been aspirated the tube was placed in the para centesis aperture with very small straight alligator forceps, under microscopic control With some experience, the prosedure lasted only a few minutes.

Subsequently the patient was usually given a 7-day course of antibiotics He then visited the outpatient clinic first at monthly intervals and later at intervals of 2—3 months Possible crusts around the tube were removed, their openness was assured and an audiometric hearing test carried out. If chronic secretory otitis media recurred after the extrusion of the tube, another tube was inserted.

The tubed patients or their parents were instructed not to let water get into the tubed ears. The patients were allowed to take a bath in a bath tub or sauna and to swim if they put cotton wool moistened in paraffin into the external meatus, but they were not allowed to dive. All respiratory infections were treated carefully The patients parents were requested to get in touch with the treating physician immediately if there was any discharge. The discharge was removed by syringing the ear with physiological saline ear drops were used locally and antibiotics orally

Data on the patients medical history on their period of hospitalization and outpatient clinic visits were obtained from case histories, and complemented if necessary in connection with the follow up examination This was carried out during the autumn of 1972 all the 181 patients of the material being invited with an attendance of 166 (91 6 %) On this occasion the present author personally carried out the otological examination of all patients using the operating microscope to help in ascertaining the drum status At the same time an audiometric hearing test for air and bone conduction was carried out on all patients over 4 years of age. Due to poor cooperation the hearing results of a number of the youngest patients were unreliable and had to be excluded from the statistical analyses The audiometric test was carried out by the two trained examiners who had made the earlier audiometric tests. All hearing level examinations were made with the Madsen Model OB 60 audiometer calibrated according to the ISO standards The results were analysed at the Oulu University Computer Centre Student s t test was used for the statistical comparison of the results.

Purulent discharge occurred during tube treatment in 124 cases (25 %) i.e. 118 ears (41 %) and 79 patients (48 %). When the bacterial culture on tube insertion was positive, discharge occurred in 55 % of the cases, and when Hemophilus influenzae grew in the bacterial culture discharge occurred in 79 % of the cases. The most common bacteria were Staphylococcus aureus (37.4 %), Diplococcus pneumoniae (12.5 %), Hemophilus influenzae (11.7 %), Staphylococcus albus (8.9 %), Escherichia coli (6.1 %), Streptococcus (5.6 %) and Pseudomonas aeruginosa (5.0 %).

4.1.1.2. Follow up study

The follow-up examination was attended by 151 patients. Four patients reported by letter that their ears were symptom-free and the hearing level, at an audiometric examination at school, had been found to be normal. Their tympanostomy tubes had been extruded, and their follow up period exceeded 2 years. Information concerning them was obtained from the record of the last visit to the outpatient clinic. Nothing was heard concerning 9 patients, who also had an outpatient follow-up period exceeding 2 years and whose tympanostomy tubes had been extruded. The information concerning them was also taken from the record of the last visit to the outpatient clinic.

The average follow-up period was 3 years 2 months (range 12 months to 7 years). During this period the tube had been removed from 19 ears after 4—6 months of treatment. In 3 of these ears, a recurrence developed within the next 6 months. In all the other patients, the tubes were allowed to extrude spontaneously and if the disease recurred a new one was inserted. Mastoidectomy was carried out during the follow-up period on 8 patients representing 15 ears for persistent discharge and on the basis of the x-ray finding. In one of these ears the discharge started immediately on insertion of the tube. At operation, the mastoid air cells of 5 ears were found to be filled with glue-like secretion, in 2 ears the mucosa of the mastoid air cells was thickened, and in 8 ears the mucosa was granulative and new bone formation was visible. After mastoidectomy there was no discharge from 4 ears, and discharge of short duration from 9 ears, but in one patient who had ozaena also, discharge was almost continuous from both ears. At the follow up the drum was normal in 10 ears, the tube still remained in 4 ears, and perforation with discharge was seen in one ear (ozaena).

The follow up showed that chronic secretory otitis media had healed completely in 190 ears (65.5 %). No tubes were left in these ears, and no signs of recurrence were observed (Table VI). Altogether chronic secretory otitis media had healed in 100 patients (69.8 %), in 68 of whom it had healed in both ears, in 22 in only one ear and in 32 in the single ear affected. The mean duration of tympanostomy tube therapy in the ears, which were found to be healthy at the time of the examination, was 11.3 months (range 1 month to 5 years) and the mean symptom free period after healing was 19 months (range 1 month to 5 years).

Table VI. *Status at the follow-up examination of the ears treated with tympanostomy*

Status at the follow-up examination	No.	%
Chronic secretory otitis media healed	190	65.5
Tympanostomy tubes in position and ventilating	64	22.1
Purulent discharge from tympanostomy tube	5	1.7
Chronic secretory otitis media recurred	9	3.1
Complications of chronic secretory otitis media and tube therapy	22	7.6
Total	290	100.0

In the ears in which chronic secretory otitis media had healed, the *appearance* of the drum was normal or nearly normal in 130 cases (68.4 %) and abnormal in 60 cases (31.6 %) (Table VII). The appearance of the drum was classified as normal if no abnormality could be observed on examination with Siegle's pneumatic speculum. The pathological drums were divided into subgroups on the basis of their microscopic appearance. The tympanostomy scar was visible

children under 1 year (18.9 %) but that of the 7—8 year olds i.e those who had just started school was almost as big (14 6 %) The mean age of onset was 4 years 10 months.

Adenotomy had been carried out earlier on 48 patients and adenotonsillectomy on 14 In the course of the treatment of chronic secretory otitis media adenotomy was performed on 129 and adenotonsillectomy on 15 patients 52 of the adenotomies were re-adenotomies No operation was made on 10 patients, 8 of whom had cleft palate one ozaena, and in one patient aged 14 years no adenoid tissue was present

On admission to hospital 24 children were found to have sinusitis and 4 allergic rhinitis There was no instance of hypo- or agamma globulinaemia but in 9 children the immunoglobulin values were at the lower limit of normal

An abnormal status of the nasopharynx was seen in 6 patients. In 2 of these the tubal orifices were severely strictured after an earlier adenotomy and in another 2 the orifices were otherwise very narrow One patient after adenotomy had developed a synechia from the soft palate to the roof of the nasopharynx and in another the tori were hypertrophic, practically filling the nasopharynx Very large-sized adenoids were found in 35 children

The mean interval from the diagnosis of secretory otitis media to the insertion of tympanostomy tubes was 8.5 months. In this interval a number of the patients were treated by weekly paracentesis, while others were symptom free for months of even years in the meantime The mean age of the patients at the time of the first insertion of tubes was 5 years 8 months The tube was inserted only once into 169 ears (58 3 %) twice into 62 ears (21 4 %) three times into 34 ears (11 7 %) and four or more times into 25 ears (8 6 %) The highest number of tympanostomy tubes per ear was 8 of which 7 were inserted in another hospital. All told 511 tubes were inserted to the patients of the present series The mean period during which the tubes remained ventilating was 7 0 months The first tube remained in position for 7 8 months on average the second for 7 2 months the third for 6 3 months and from the fourth onwards for 6 0 months The shortest period was 48 hours after which the tube was extruded with purulent discharge and the longest 56 months. Tympanotomy had to be carried out twice after the inserted tube had slipped into the tympanum. Both ears healed without complications.

In the preliminary examinations a sample was taken in connection with paracentesis for bacterial analysis The cultures of these samples were always negative in 74 ears (25.5 %) None of these patients had been treated with antibiotics immediately before paracentesis

In connection with the insertion of the tympanostomy tube a bacterial sample was taken under operating-microscope control direct from the paracentesis opening The external meatus was only mechanically cleaned before the procedure. A total of 322 bacterial samples (198 ears) were taken in connection with 511 tube insertions. The bacterial culture of 251 samples (78 %) was negative and that of 71 samples (22 %) positive. The most common bacteria were Hemophilus influenzae Staphylococcus aureus and Staphylococcus albus (Table V)

Table V *Results of bacterial analysis of samples taken in connection with insertion of the tubes*

Organism	No	% of positive cultures
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4.1.1.3. Case reports of complicated cases

4.1.1.3.1 Dry perforation, 8 patients (8 ears)

1 S.L. 21 years. The patient sought treatment at the age of 14 for impaired hearing. There was no history of otitis, and on admission the hearing level of the right ear was 31 7 dB and of the left 33.3 dB (means of the 500, 1000 and 2000 Hz thresholds). Paracentesis showed mucoid secretion on repeated occasions. Tympanostomy tubes ere inserted 3 times into both ears. At the follow-up examination the right-ear tube was in the external meatus, the drum showed a central perforation of 2 mm in diameter and the ear s dry In the left drum the tube was in position. The hearing level of the right ear was 15.0 dB, of the left 5.0 dB.

2. P.L 12 years. Impaired hearing was diagnosed at the age of 4 years. Adenotomy was performed but the hearing still remained impaired. A the age of 8, tubes were inserted into both ears. The hearing level prior to tube insertion as on the right 45.0 dB and on the left 13.3 dB. The left ear remained symptom-free after the extrusion of the tube, but in the right the tube had to be re-inserted 5 times. At the follow-up examination dry central perforation of 2 mm in diameter was noted in the right drum, while the left drum was normal. Both ears had the same hearing level, 3.3 dB.

3. T.A. 7 years. Adenotonsillectomy was performed at the age of 3 for recurrent tonsillitis. At the age of 5 the patient was again brought for treatment, this time for impaired hearing. The hearing level on admission s 18.3 dB in the right and 21.7 dB in the left ear Tympanostomy tubes were inserted into both ears. There was discharge from the ears and the tubes were extruded. The patient failed to attend the outpatient clinic, and was brought in for treatment one year later for discharge from both ears. The left ear healed with conservative therapy but in the right ear dry central perforation persisted. At the follow-up examination 6 months later the right ear had dry perforation of 3 mm in diameter and the left drum showed rigid mobility but paracentesis was negative. The hearing level of the right ear was 18.3 dB and of the left 33.3 dB.

4 S K 12 years. The patient had undergone adenotonsillectomy at the age of 3. Treatment was required again at the age of 6 for impaired hearing. The hearing level of the right ear was 31 7 dB, of the left 11 7 dB. Tympanostomy tubes were inserted twice into both ears At the follow-up examination the right drum was normal, but the left drum had a dry central perforation of 2 mm in diameter The hearing level of the right ear was 15.0 dB of the left 11 7 dB.

5. L.V 3 years. The patient came for treatment at the age of 1 year for recurrent otitis. Paracentesis produced repeatedly glue-like secretion. Tympanostomy tubes were inserted into both ears at the age of 14 months. After the insertion discharge continued for a long time from both ears, and at the age of 18 months ozaena was additionally diagnosed in the patient. Mastoidectomy of both ears was carried out at the age of 20 months for discharge and radiographic mastoiditis. Even then there was discharge from both ears from time to time. At the follow-up examination the tube in the right ear was in position and the ear was dry while a relatively extensive dry central perforation was noted in the left drum. Severe ozaena persisted in the nose.

6. R.V 15 years. The patient had had impaired hearing since the age of 9 He sought treatment at the age of 10 when the hearing level of the right ear was 35.0 dB and of the left 63.3 dB. Tubes were inserted into both ears. The left one was soon extruded, and a perforation along the posterior margin remained in the ear Later the tube of the right ear was also extruded, and a dry central perforation remained. A modified radical operation was later carried out on the left ear where necrosis of the long process of the incus was found. Reconstruction was effected with a steel wire columella. At the follow-up examination the right drum showed an extensive dry perforation and the left ear mobile drum. The hearing level of the right ear was 31 7 dB and of the left 16.7 dB.

7 A.O 19 years. Discharge from both ears appeared at the age of 13. A year later the patient sought treatment for impaired hearing. On admission the hearing level of the right ear was 23.3 dB and of the left 18.3 dB. Tympanostomy tubes ere inserted into both ears. Both ere extruded within six months, and a dry central perforation of 2 mm in diameter remained in the left ear hereas the right drum was normal at the follow-up examination. The hearing level of the right ear was 11.7 dB, of the left 26.7 dB.

8. T K. 11 years. Impaired hearing of both ears was diagnosed at the age of 8. Adenotomy was performed but hearing remained poor Six months later tympanostomy tubes were inserted into both ears. The tubes were extruded within 6 months, and dry perforation remained in the right ear Since the perforation failed to close within a year and since there was no sign of chronic secretory otitis media, myringoplasty was undertaken. At the follow-up examination one year later both drums were intact, and the hearing level of the right ear was 13.3 dB, of the left 6.7 dB.

Table VII Eardrum appearance in the ears with healed chronic secretory otitis media (changes not mutually excluding)

Eardrum appearance	No	
Tympanosclerotic	29	
Pseudomembranous	22	
Visible tympanostomy scar	15	
Retracted	6	
Atrophic	3	
Adherent to the head of the stapes	3	
Abnormal		60
Normal or nearly normal		130
Total		190

on the cicatricial drums, while in the atrophic either the whole drum or its posterosuperior segment was atrophied.

In 64 ears (22.1 %) the tube was still in position and ventilating and the patients had no symptoms of the disease. In these 64 ears the tympanostomy tube therapy had lasted 24 2 months on average. Purulent discharge from the tympanostomy tube was observed in the follow up study from 5 ears (1 7 %) In 9 ears (3 2 %) chronic secretory otitis media was found to have recurred, while 22 ears (7 6 %) showed complications (Table VIII) The most common was drum perforation in 12 ears. Seven of the perforations were dry and 5 had discharge

Table VIII *Complications of chronic secretory otitis media and tympanostomy tube treatment recorded at the follow-up examination*

Complication	No
Drum perforation dry	7
Drum perforation, with discharge	5
Drum perforation, operated	1
Retracted drum	2
Partly adhesive drum	2
Attic cholesteatoma	2
Tympanic cholesteatoma, operated	2
Necrosis of the long process of incus, operated	1
Total	22

Furthermore, myringoplasty had been performed during the follow up period in one ear of persistent perforation. In the total material therefore the number of perforations following tube therapy was 13 (4.5 %) Two drums (0 7 %) were grossly retracted (para centesis was negative) and 2 drums (0 7 %) partly adhesive to the promontorium One patient had attic cholesteatoma in both ears (0 7 %) although the tympanostomy tubes on both sides were in position and ventilating During the follow up period, a modified radical operation had been performed on 2 ears (0 7 %) for a cholesteatoma of the posterosuperior segment. One ear (0 35 %) had been treated with tympanotomy and the finding was necrosis of the long process of the incus.

Eighteen patients and a total of 35 ears had been treated with tympanostomy tubes for over 2 years The mean period of treatment for these patients was 33 8 months (range 24—60 months) The cleft palate operation had been performed on 3 the orifices of the Eustachian tubes were badly strictured after adenotomy in 2, and one had a severe allergic rhinitis. No causative factor necessitating the extended tube therapy could be demonstrated in 12 patients (23 ears)

During the follow up period, tympanotomy had been made on one ear and it had been found that the stapes was underneath the bifurcate facial nerve and failed to connect with the long process of the incus. No reconstruction was possible.

No differences between age groups 0—5 and 6—14 years were observable in the results of tube therapy 41 9 % of the 76 patients aged 0—5 years at the time of first insertion of the tube, and 43.3 % of the 88 patients who were 6—14 years old at the time of the first insertion, were symptom free after one year Nor could any great differences be observed between the greatest age groups, 0—1 and 7—8 years. Of the former age group 42.8 % and of the latter 47 4 % were symptom free after one year

4.1.1.3. Case reports of complicated cases

4.1.1.3.1. Dry perforation, 8 patients (8 ears)

1. S.L. 21 years. The patient sought treatment at the age of 14 for impaired hearing. There was no history of otitis, and on admission the hearing level of the right ear was 31.7 dB and of the left 33.3 dB (means of the 500, 1000 and 2000 Hz thresholds). Paracentesis showed mucoid secretion on repeated occasions. Tympanostomy tubes were inserted 3 times into both ears. At the follow-up examination the right-ear tube was in the external meatus, the drum showed a central perforation of 2 mm in diameter and the ear was dry. In the left drum the tube was in position. The hearing level of the right ear was 15.0 dB, of the left 5.0 dB.

2. P.J. 12 years. Impaired hearing was diagnosed at the age of 4 years. Adenotomy was performed but the hearing still remained impaired. At the age of 8, tubes were inserted into both ears. The hearing level prior to tube insertion was on the right 45.0 dB and on the left 13.3 dB. The left ear remained symptom-free after the extrusion of the tube, but in the right the tube had to be re-inserted 5 times. At the follow-up examination a dry central perforation of 2 mm in diameter was noted in the right drum, while the left drum was normal. Both ears had the same hearing level, 3.3 dB.

3. T.A. 7 years. Adenotonsillectomy was performed at the age of 3 for recurrent tonsillitis. At the age of 5 the patient was again brought for treatment, this time for impaired hearing. The hearing level on admission was 18.3 dB in the right and 21.7 dB in the left ear. Tympanostomy tubes were inserted into both ears. There was discharge from the ears and the tubes were extruded. The patient failed to attend the outpatient clinic, and was brought in for treatment one year later for discharge from both ears. The left ear healed with conservative therapy but in the right ear a dry central perforation persisted. At the follow-up examination 6 months later the right ear had a dry perforation of 3 mm in diameter and the left drum showed rigid mobility but paracentesis was negative. The hearing level of the right ear was 18.3 dB and of the left 33.3 dB.

4. S.K. 12 years. The patient had undergone adenotonsillectomy at the age of 3. Treatment was required again at the age of 6 for impaired hearing. The hearing level of the right ear was 31.7 dB, of the left 11.7 dB. Tympanostomy tubes were inserted twice into both ears. At the follow-up examination the right drum was normal, but the left drum had a dry central perforation of 2 mm in diameter. The hearing level of the right ear was 15.0 dB, of the left 11.7 dB.

5. L.V. 3 years. The patient came for treatment at the age of 1 year for recurrent otitis. Paracentesis produced repeatedly glue-like secretion. Tympanostomy tubes were inserted into both ears at the age of 14 months. After the insertion discharge continued for a long time from both ears, and at the age of 18 months eczema was additionally diagnosed in the patient. Mastoidectomy of both ears was carried out at the age of 20 months for discharge and radiographic mastoiditis. Even then there was discharge from both ears from time to time. At the follow-up examination the tube in the right ear was in position and the ear was dry, while a relatively extensive dry central perforation was noted in the left drum. Severe eczema persisted in the nose.

6. R.V. 15 years. The patient had had impaired hearing since the age of 9. He sought treatment at the age of 10 when the hearing level of the right ear was 35.0 dB and of the left 43.3 dB. Tubes were inserted into both ears. The left one was soon extruded, and a perforation along the posterior margin remained in the ear. Later the tube of the right ear was also extruded, and a dry central perforation remained. A modified radical operation was later carried out on the left ear where necrosis of the long process of the incus was found. Reconstruction was effected with a steel wire columella. At the follow-up examination the right drum showed an extensive dry perforation and the left ear a mobile drum. The hearing level of the right ear was 31.7 dB and of the left 16.7 dB.

7. A.O. 19 years. Discharge from both ears appeared at the age of 13. A year later the patient sought treatment for impaired hearing. On admission the hearing level of the right ear was 23.3 dB and of the left 18.3 dB. Tympanostomy tubes were inserted into both ears. Both were extruded within six months, and a dry central perforation of 2 mm in diameter remained in the left ear whereas the right drum was normal at the follow-up examination. The hearing level of the right ear was 11.7 dB, of the left 26.7 dB.

8. T.K. 11 years. Impaired hearing of both ears was diagnosed at the age of 8. Adenotomy was performed but hearing remained poor. Six months later tympanostomy tubes were inserted into both ears. The tubes were extruded within 6 months, and a dry perforation remained in the right ear. Since the perforation failed to close within a year and since there was no sign of chronic secretory otitis media, myringoplasty was undertaken. At the follow-up examination one year later both drums were intact, and the hearing level of the right ear was 13.3 dB, of the left 6.7 dB.

Table VII *Eardrum appearance in the ears with healed chronic secretory otitis media (changes not mutually excluding)*

Eardrum appearance	No.	
Tympanosclerotic	29	
Pseudomembranous	22	
Visible tympanostomy scar	15	
Retracted	6	
Atrophic	3	
Adherent to the head of the stapes	3	
Abnormal		60
Normal or nearly normal		*130*
Total		190

on the cicatricial drums while in the atrophic either the whole drum or its posterosuperior segment was atrophied

In 64 ears (22.1 %) the tube was still in position and ventilating and the patients had no symptoms of the disease In these 64 ears the tympanostomy tube therapy had lasted 24 2 months on average. Purulent discharge from the tympanostomy tube was observed in the follow up study from 5 ears (1 7 %) In 9 ears (3 2 %) chronic secretory otitis media was found to have recurred, while 22 ears (7 6 %) showed complications (Table VIII) The most common was drum perforation in 12 ears. Seven of the perforations were dry and 5 had discharge.

Table VIII *Complications of chronic secretory otitis media and tympanostomy tube treatment recorded at the follow-up examination*

Complication	No.
Drum perforation dry	7
Drum perforation, with discharge	5
Drum perforation, operated	1
Retracted drum	2
Partly adhesive drum	2
Attic cholesteatoma	2
Tympanic cholesteatoma, operated	2
Necrosis of the long process of incus, operated	1
Total	22

Furthermore, myringoplasty had been performed during the follow up period in one ear of persistent perforation In the total material therefore the number of perforations following tube therapy was 13 (4.5 %) Two drums (0 7 %) were grossly retracted (para centesis was negative) and 2 drums (0 7 %) partly adhesive to the promontorium. One patient had attic cholesteatoma in both ears (0 7 %) although the tympanostomy tubes on both sides were in position and ventilating. During the follow up period, a modified radical operation had been performed on 2 ears (0.7 %) for a cholesteatoma of the posterosuperior segment. One ear (0.35 %) had been treated with tympanotomy and the finding was necrosis of the long process of the incus.

Eighteen patients and a total of 35 ears had been treated with tympanostomy tubes for over 2 years. The mean period of treatment for these patients was 33 8 months (range 24—60 months) The cleft palate operation had been performed on 3 the orifices of the Eustachian tubes were badly strictured after adenotomy in 2, and one had a severe allergic rhinitis. No causative factor necessitating the extended tube therapy could be demonstrated in 12 patients (23 ears)

During the follow up period, tympanotomy had been made on one ear and it had been found that the stapes was underneath the bifurcate facial nerve and failed to connect with the long process of the incus. No reconstruction was possible.

No differences between age groups 0—5 and 6—14 years were observable in the results of tube therapy 41 9 % of the 76 patients aged 0—5 years at the time of first insertion of the tube and 43.3 % of the 88 patients who were 6—14 years old at the time of the first insertion were symptom-free after one year Nor could any great differences be observed between the greatest age groups 0—1 and 7—8 years. Of the former age group 42.8 % and of the latter 47 4 % were symptom free after one year

4.1.1.3. Case reports of complicated cases

4.1.1.3.1. Dry perforation, 8 patients (8 ears)

1. S.L. 21 years. The patient sought treatment at the age of 14 for impaired hearing. There was no history of otitis, and on admission the hearing level of the right ear was 31.7 dB and of the left 33.3 dB (means of the 500, 1000 and 2000 Hz thresholds). Paracentesis showed mucoid secretion on repeated occasions. Tympanostomy tubes were inserted 3 times into both ears. At the follow-up examination the right-ear tube ...as in the external meatus, the drum showed a ...ntral perforation of 2 mm in diameter and the ear ...as dry. In the left drum the tube was in position. The ...earing level of the right ear was 15.0 dB, of the left ...0 dB.

2. P.J. 12 years. Impaired hearing was diagnosed at ...he age of 4 years. Adenotomy was performed but the ...earing still remained impaired. At the age of 8, tubes ...ere inserted into both ears. The hearing level prior to ...the insertion was on the right 45.0 dB and on the left 13.3 dB. The left ear remained symptom-free after the extrusion of the tube, but in the right the tube had to be re-inserted 5 times. At the follow-up examination a dry central perforation of 2 mm in diameter was noted in the right drum, while the left drum was normal. Both ears had the same hearing level, 3.3 dB.

3. T.A. 7 years. Adenotonsillectomy was performed at the age of 3 for recurrent tonsillitis. At the age of 5 the patient was again brought for treatment, this time for impaired hearing. The hearing level on admission was 18.3 dB in the right and 21.7 dB in the left ear. Tympanostomy tubes were inserted into both ears. There was discharge from the ears and the tubes were extruded. The patient failed to attend the outpatient clinic, and was brought in for treatment one year later for discharge from both ears. The left ear healed with conservative therapy but in the right ear a dry central perforation persisted. At the follow-up examination 6 months later the right ear had a dry perforation of 3 mm in diameter and the left drum showed rigid mobility but paracentesis was negative. The hearing level of the right ear was 18.3 dB and of the left 33.3 dB.

4. S.K. 12 years. The patient had undergone adenotonsillectomy at the age of 3. Treatment was required again at the age of 6 for impaired hearing. The hearing level of the right ear was 31.7 dB, of the left 11.7 dB. Tympanostomy tubes were inserted twice into both ears. At the follow-up examination the right drum was normal but the left drum had dry central perforation of 2 mm in diameter. The hearing level of the right ear was 15.0 dB of the left 11.7 dB.

5. L.V. 3 years. The patient came for treatment at the age of 1 year for recurrent otitis. Paracentesis produced repeatedly glue-like secretion. Tympanostomy tubes were inserted into both ears at the age of 14 months. After the insertion discharge continued for a long time from both ears, and at the age of 18 months ozaena was additionally diagnosed in the patient. Mastoidectomy of both ears was carried out at the age of 20 months for discharge and radiographic mastoiditis. Even then there was discharge from both ears from time to time. At the follow-up examination the tube in the right ear was in position and the ear was dry while relatively extensive dry central perforation was noted in the left drum. Severe ozaena persisted in the nose.

6. R.V. 15 years. The patient had had impaired hearing since the age of 9. He sought treatment at the age of 10 when the hearing level of the right ear was 35.0 dB and of the left 63.3 dB. Tubes were inserted into both ears. The left one was soon extruded, and a perforation along the posterior margin remained in the ear. Later the tube of the right ear was also extruded, and a dry central perforation remained. A modified radical operation was later carried out on the left ear where necrosis of the long process of the incus was found. Reconstruction was effected with steel wire columella. At the follow-up examination the right drum showed an extensive dry perforation and the left ear a mobile drum. The hearing level of the right ear was 31.7 dB and of the left 16.7 dB.

7. A.O. 19 years. Discharge from both ears appeared at the age of 13. A year later the patient sought treatment for impaired hearing. On admission the hearing level of the right ear was 23.3 dB and of the left 18.3 dB. Tympanostomy tubes were inserted into both ears. Both were extruded within six months, and dry central perforation of 2 mm in diameter remained in the left ear whereas the right drum was normal at the follow-up examination. The hearing level of the right ear was 11.7 dB, of the left 26.7 dB.

8. T.K. 11 years. Impaired hearing of both ears was diagnosed at the age of 8. Adenotomy was performed but hearing remained poor. Six months later tympanostomy tubes ere inserted into both ears. The tubes were extruded within 6 months, and dry perforation remained in the right ear. Since the perforation failed to close within year and since there was no sign of chronic secretory otitis media, myringoplasty was undertaken. At the follow-up examination one year later both drums were intact, and the hearing level of the right ear was 13.3 dB, of the left 6.7 dB.

4 1 1.3 2. Perforation with discharge, 4 patients (5 ears)

1 T N 14 years. At the age of 9 the hearing was found to be impaired, 15 0 dB in the right ear and 30 0 dB in the left. Adenotomy did not improve hearing and six months later tympanostomy tubes were inserted. The patient neglected treatment of the transient discharge from the ears At the follow up examination the right drum was found to be normal whereas in the left ear there was an extensive central perforation with discharge Bacterial culture showed a growth of E. coli, and radiography disclosed small sclerotic mastoid air cells also in the left ear The hearing level of the right ear was 6 7 dB of the left 36 7 dB

2. R.R. 15 years. The patient s hearing had been impaired since childhood, and adenotonsillectomy had been carried out at the age of 7 Even then the hearing remained impaired but the patient failed to seek treatment. He consulted the otologist next at the age of 11 when the hearing level of the right ear was 25 0 dB and of the left 28.3 dB He again failed to seek treatment, and the hearing remained poor Two years later he was seen again and the hearing level of the right ear was 25 0 dB of the left 21 7 dB. Tympanostomy tubes were then inserted into both ears. There was discharge from both ears and the tubes had to be re-inserted one year later Even then the discharge continued from both ears, but was not treated and the tubes were extruded At the follow-up examination 3 months later the right drum was normal the left ear showed a small moist central perforation on bacterial culture grew Klebsiella pneumoniae, and a number of sclerotic mastoid air cells were seen in the radiogram. The hearing level of the right ear was 1 7 dB of the left 31 7 dB

3. M.T 5 years. The patient was a mongoloid severely mentally retarded Tympanostomy tubes were inserted into both ears at the age of 4 years for chronic secretory otitis media. The tubes were extruded relatively soon after the operation and purulent discharge occurred. At the follow up examination a year later small central perforations with discharge were noted in both ears. Pseudomonas aeruginosa grew in both ears on bacterial culture.

4 O N 11 years. Adenotonsillectomy was carried out at the age of 5 One year later the patient was seen for impaired hearing Tympanostomy tubes were inserted into both ears. After extrusion of the tubes the ears remained symptom-free for 2 years, after which the left ear showed discharge. At the follow up examination the right drum was found to be normal, the left showed a small central perforation with discharge. Staphylococcus aureus grew on bacterial culture.

4 1 1.3 3 Attic cholesteatoma, 1 patient (2 ears)

1 H H 11 years. Impaired hearing was discovered at the age of 7 when adenotomy was carried out. Even after this the hearing remained impaired, and tonsillectomy was carried out at the age of 8. The hearing was still impaired In the right ear it was 15.0 dB and in the left 30 0 dB. Tubes were inserted into both ears. Extrusion of both tubes occurred 7 months later and the ears remained symptom free for 5 months, after which the disease recurred and both ears had to be re-fitted with tubes. Six months later the left-ear tube was extruded and a new one was re-inserted Purulent discharge from the left ear persisted for about a fortnight. One year later tubes again had to be re-inserted into both ears. On this occasion, an attic cholesteatoma was diagnosed in both ears and its removal through the external meatus was not entirely successful At the follow-up examination cholesteatomas were diagnosed in both attic regions. The hearing level of the right ear was 10.0 dB and of the left similarly 10 0 dB The tubes were in position in both ears.

An atticoantrotomy of the left ear was carried out after the follow-up examination. It revealed a cholesteatoma approximately the size of a pea, situated partly under and partly on top of the ossicular chain Reconstruction of the auditory ossicles was effected by placing the incus onto the head of the stapes. After the operation the hearing level of the left ear was 35 0 dB

4 1 1 3 4 Cholesteatoma of the posterosuperior segment 2 patients (2 ears)

1 M M 16 years. The patient had had ear trouble ever since the age of 10 He was first seen at the age of 12 when adenotomy was carried out and a tympanostomy tube inserted into the left ear Preoperatively the hearing level of the left ear was 68.3 dB. The tube was extruded within a few months. A marginal perforation and a cholesteatoma were seen in the region of the posterosuperior segment of the drum (the cholesteatoma had apparently been there even before the insertion of the tube) A modified radical operation was made 6 months later and a cholesteatoma entering the antrum was seen. At the follow-up examination the right ear was found to have a normal drum while that

of the left ear showed reduced mobility The hearing level of the right ear as 3.3 dB and of the left 36.7 dB.

2. R.V 15 years. Impaired hearing was discovered at the age of 9 The patient was first seen at the age of 10. The right ear was found to have a drum of reduced mobility and the left ear one that was practically adhesive. The hearing level of the right ear was 35.0 dB and of the left 63.3 dB. Tympanostomy tubes were inserted into both. Discharge from the left ear was noted. A perforation along the posterior margin remained in the drum. T o years later a cholesteatoma was found, extending to the antrum, and there was necrosis of the long process of the incus. Reconstruction of the auditory ossicles was effected with steel wire columella. At the follow-up examination the right drum showed a dry perforation hile the left drum as intact and mobile. The hearing level of the right ear was 31 7 dB and of the left, 16.7 dB.

4 1.1.3.5. Conductive hearing defect, 1 patient, (2 ears)

1. S.T 9 years. The patient was first examined for impaired hearing at the age of 5. Even after an adenotomy the hearing remained impaired, although the movement of the drums was moderately good, and only little fluid was aspirated by paracentesis. Tympanostomy tubes were inserted into both ears one year later Paracentesis as now bilaterally negative. Within less than a year the tubes were extruded, and the drums of both ears showed good mobility At the follow-up examination both drums showed normal mobility The hearing level of the right ear was 35.0 dB, of the left 31 7 dB. The bone conduction hearing of both ears was on the zero level. This defect was suspected to depend on bilateral tympanal anomaly but no ultimate cause can be verified until tympanotomy is carried out

4 1 2. Patients treated without tympanostomy

The group comprised 17 children with chronic secretory otitis media. In 16 the disease was bilateral and in one unilateral. The material therefore consisted of 33 ears. There were 10 boys (59 %) and 7 girls (41 %)

4 1.2.1 Preoperative history and data from the time of treatment

The chronic secretory otitis media of the patients of this group was treated with repeated paracentesis and adenotomy or adenotonsillectomy but the treatment was not completed since 13 patients failed to attend the outpatient clinic and the attendance of 4 patients was no longer considered necessary after a symptom-free period (c. 1 month) which, in retrospect, seems too short.

The patients had earlier been healthy Only 3 had had recurrent tonsillitis, while 8 children had had episodes of acute otitis media, and 4 had had discharge from the ear Five children had no previous history of otitis media.

The onset of the symptoms of secretory otitis media had occurred at the mean age of 7 years 4 months (range 6 months to 9 years)

Adenotomy had previously been carried out on 6 children. During the course of treatment, 8 children underwent adenotomy and 9 adenotonsillectomy (including some that had earlier undergone adenotomy) On admission 3 children had sinusitis, one allergic rhinitis and 2 had adenoids obstructing the nasopharynx.

The duration of treatment, on average, was 6.1 months (range 1 month to 22 months) during which time the patients were treated if required with paracentesis and courses of antibiotics. At the last visit to the outpatient clinic the appearance and mobility of the drum were normal in 7 ears, whereas in 7 ears the drum had reduced mobility and paracentesis produced a glue-like effusion. In connection with paracentesis, 50 samples (30 ears) were taken for bacterial culture. The culture was negative on 37 samples (74 %) and positive on 13 (26 %) The verified bacteria were Staphylococcus albus (46.2 %) Staphylococcus aureus (23 1 %) Streptococcus (23 1 %) and Hemophilus influenzae (7 6 %)

4 1 1.3 2. Perforation with discharge 4 patients (5 ears)

1 T.N 14 years. At the age of 9 the hearing was found to be impaired 15 0 dB in the right ear and 30.0 dB in the left Adenotomy did not improve hearing and six months later tympanostomy tubes were inserted. The patient neglected treatment of the transient discharge from the ears. At the follow-up examination the right drum was found to be normal whereas in the left ear there was an extensive central perforation with discharge. Bacterial culture showed a growth of E coli, and radiography disclosed small sclerotic mastoid air cells also in the left ear The hearing level of the right ear was 6.7 dB of the left 36 7 dB

2. R.R. 15 years. The patient s hearing had been impaired since childhood and adenotonsillectomy had been carried out at the age of 7 Even then the hearing remained impaired but the patient failed to seek treatment He consulted the otologist next at the age of 11 when the hearing level of the right ear was 25 0 dB, and of the left 28.3 dB He again failed to seek treatment, and the hearing remained poor Two years later he was seen again and the hearing level of the right ear was 25 0 dB of the left 21 7 dB. Tympanostomy tubes were then inserted into both ears. There was discharge from both ears and the tubes had to be re inserted one year later Even then the discharge continued from both ears, but was not treated and the tubes were extruded. At the follow-up examination 3 months later the right drum was normal the left ear showed a small, moist central perforation on bacterial culture grew Klebsiella pneumoniae and a number of sclerotic mastoid air cells were seen in the radiogram. The hearing level of the right ear was 1 7 dB of the left 31 7 dB

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4 1 1.3 3 Attic cholesteatoma 1 patient (2 ears)

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An atticoantrotomy of the left ear was carried out after the follow up examination. It revealed a cholesteatoma approximately the size of a pea, situated partly under and partly on top of the ossicular chain Reconstruction of the auditory ossicles was effected by placing the incus onto the head of the stapes. After the operation the hearing level of the left ear was 35 0 dB

4 1 1.3 4 Cholesteatoma of the posterosuperior segment 2 patients (2 ears)

1 M M. 16 years. The patient had had ear trouble ever since the age of 10 He was first seen at the age of 12 when adenotomy was carried out and a tympanostomy tube inserted into the left ear Preoperatively the hearing level of the left ear was 68.3 dB. The tube was extruded within a few months. A marginal perforation and a cholesteatoma were seen in the region of the posterosuperior segment of the drum (the cholesteatoma had apparently been there even before the insertion of the tube) A modified radical operation was made 6 months later and a cholesteatoma entering the antrum was seen. At the follow-up examination the right ear was found to have a normal drum while that

4.2. HEARING RESULTS

4.2.1. *Total material*

The hearing results presented under this heading cover all the patients of the present material whose hearing could be reliably measured.

Table X. Hearing level in 95 patients with chronic secretory otitis media on admission. The air conduction figures are mean values for 161 ears, bone conduction figures those for 122 ears

Frequency	Hearing level (dB)			
	Air conduction		Bone conduction	
(Hz)	Mean	S.D	Mean	S.D
125	28.7	11.4		
250	27.4	12.4	4.6	5.2
500	29.6	12.7	4.0	6.0
1000	30.1	13.8	3.2	7.5
2000	23.0	12.0	1.7	7.4
4000	28.8	14.5	3.4	8.6
6000	31.9	14.9		
8000	33.8	14.6		

On admission the hearing level could be measured in 95 patients with chronic secretory otitis media, representing 161 ears. The mean values and standard deviations of the air and bone conduction thresholds at different frequencies are presented in Table X. The mean air conduction threshold of the speech frequencies of the total material (mean value of the thresholds of 500 1000 and 2000 Hz) was 27.6 dB (S.D 12.8) the corresponding mean bone conduction threshold 3.0 dB (S.D 7 1) and the mean air-bone gap 24 6 dB. The youngest of the patients examined with audiometry was 4 years, and the mean age was 8.6 years. The mean air conduction threshold at 2000 Hz of the total material was statistically significantly better ($p < 0.01$) than the mean air conduction threshold at 250 Hz and highly significantly ($p < 0.001$) better than at the other frequencies. Statistically significant differences could not be recorded in the bone conduction thresholds.

Table XI. Hearing level in 146 patients with chronic secretory otitis media at the follow-up examination. The air conduction figures are mean values for 238 ears, bone conduction figures those for 40 ears.

Frequency	Hearing level (dB)			
	Air conduction		Bone conduction	
(Hz)	Mean	S.D	Mean	S.D
125	17.4	10.8		
250	15.2	10.7	7.1	5.3
500	14.0	11.5	3.5	4.5
1000	12.9	11.8	5.5	7.5
2000	10.0	11.1	3.9	9.2
4000	14.2	12.3	7.4	8.0
6000	19.2	13.9		
8000	20.7	15.1		

At the follow-up examination, on average 3 years 2 months later the hearing examination could be reliably carried out on 146 patients, and a total of 238 ears. The mean values and standard deviations of the air and bone conduction thresholds at different frequencies are presented in Table XI The mean air conduction threshold at speech frequencies was 12.3 dB (S.D 11.5) the corresponding mean bone conduction value

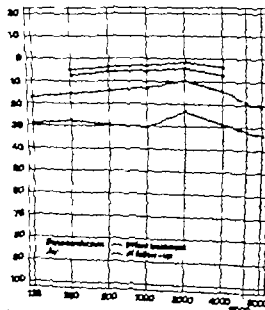


Fig. 2. The mean audiogram of the total material before treatment (161 ears) and at follow-up (238 ears).

4 1 2.2. Follow up study

The follow up examination was attended by 15 patients who had had chronic secretory otitis media in a total of 29 ears Two patients both with bilateral disease, failed to attend One of them wrote a letter stating that he had had no ear trouble since his last visit to the outpatient clinic and that his hearing acuity had been found normal at the audiometric examination at school The data concerning this patient were taken from the record of his last visit to the outpatient clinic when the drum status had been normal and the hearing level good in both ears, and the patient had been symptom-free for a year

The mean follow up period was 4 years 7 months (range 3 years 3 months to 7 years 3 months)

Table IX *Eardrum appearance at the follow up examination of the ears treated without tympanostomy*

Eardrum appearance	No
Retracted	2
Atrophic	2
Tympanosclerotic	1
Pseudomembranous	1
Totally adhesive	2
Abnormal, total	8
Normal or nearly normal	23
Total	31

In no ear was chronic secretory otitis media found at the follow up examination. The drum appearance was normal or nearly normal in 23 ears (74 2 %) and abnormal in 8 ears (25 8 %) (Table IX) In 2 ears (6.5 %) the drum was retracted and in another 2 (6.5 %) atrophic. Tympanosclerosis was diagnosed in 1 drum (3 2 %) and 1 drum (3 2 %) was pseudomembranous In one patient both drums (6.5 %) were totally adhesive except at the tubal orifice where there was bilaterally a small air-containing area. The treatment of this patient had been irregular ever since the beginning and the patient had failed to attend the outpatient clinic.

The mobility of the drum at the follow-up examination was normal or nearly normal in 27 ears (87 %) reduced in 2 ears (6.5 %) (paracentesis negative in both) and in the 2 ears mentioned above (6.5 %) the drum was adhesive.

4 1 2.3 Case reports of complicated cases

4 1 2.3 1 Drum of reduced mobility 1 patient (2 ears)

I S K 15 years. Since the age of 7 the hearing of both ears had been impaired. The patient was first seen at the age of 8 when both drums showed reduced mobility and paracentesis produced a glue-like effusion On admission the hearing level of the right ear was 33.3 dB and of the left ear 30 0 dB. Adenotomy was carried out 2 months later Following this the patient failed to attend the outpatient clinic. At a follow up examination 3 years later both drums were found to be thickened and of greatly reduced mobility Paracentesis was bilaterally negative. The hearing level of the right ear was 30 0 dB and of the left ear 13.3 dB.

4 1 2.3 2 Adhesive drum, 1 patient (2 ears)

I K.R. 14 years. At the age of 10 the patient had had discharge from both ears, and the hearing had subsequently been impaired. The patient was first seen one year later and at that time the right drum had a small perforation with discharge while the left drum showed reduced mobility The hearing level of the right ear was 38.3 dB and of the left ear 35 0 dB. After adenotomy had been performed, the left ear was symptom-free but transient purulent discharge occurred from the right ear Some 6 months after the adenotomy both drums showed reduced mobility and paracentesis yielded a glue-like effusion. The hearing level of the right ear was now 31 7 dB and of the left ear 30 0 dB After this the patient failed to visit the outpatient clinic, and there was discharge from the ears which was left untreated At the follow-up examination the drums were found to be adhesive except at the tubal orifice where both ears showed a small air-containing area. Radiography disclosed mastoid air cells that were almost completely sclerosed The hearing level of the right ear was 51 7 dB and of the left ear similarly 51 7 dB.

4.2. HEARING RESULTS

4.2.1 *Total material*

The hearing results presented under this heading cover all the patients of the present material whose hearing could be reliably measured.

Table X. *Hearing level in 95 patients with chronic secretory otitis media on admission. The air conduction figures are mean values for 161 ears, bone conduction figures those for 122 ears*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	28.7	11.4		
250	27.4	12.4	4.6	5.2
500	29.6	12.7	4.0	6.0
1000	30.1	13.8	3.2	7.5
2000	23.0	12.0	1.7	7.4
4000	28.8	14.5	3.4	8.6
6000	31.9	14.9		
8000	33.8	14.6		

On admission, the hearing level could be measured in 95 patients with chronic secretory otitis media, representing 161 ears. The mean values and standard deviations of the air and bone conduction thresholds at different frequencies are presented in Table X. The mean air conduction threshold of the speech frequencies of the total material (mean value of the thresholds of 500, 1000 and 2000 Hz) was 27.6 dB, (S.D 12.8) the corresponding mean bone conduction threshold 3.0 dB (S.D 7.1) and the mean air-bone gap 24.6 dB. The youngest of the patients examined with audiometry was 4 years, and the mean age was 8.6 years. The mean air conduction *threshold* at 2000 *Hz* of the total material was statistically significantly better ($p<0.01$) than the mean air conduction threshold at 250 Hz and highly significantly ($p<0.001$) better than at the other frequencies. Statistically significant differences could not be recorded in the bone conduction thresholds.

Table XI. *Hearing level in 146 patients with chronic secretory otitis media at the follow-up examination. The air conduction figures are mean values for 238 ears, bone conduction figures those for 40 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	17.4	10.8		
250	15.2	10.7	7.1	5.3
500	14.0	11.5	5.5	4.5
1000	12.9	11.8	5.5	7.5
2000	10.0	11.1	3.9	9.2
4000	14.2	12.3	7.4	8.0
6000	19.2	13.9		
8000	20.7	15.1		

At the follow-up examination, on average 3 years 2 months later the hearing examination could be reliably carried out on 146 patients, and a total of 238 ears. The mean values and standard deviations of the air and bone conduction thresholds at different frequencies are presented in Table XI. The mean air conduction threshold at speech frequencies was 12.3 dB (S.D 11.5) the corresponding mean bone conduction value

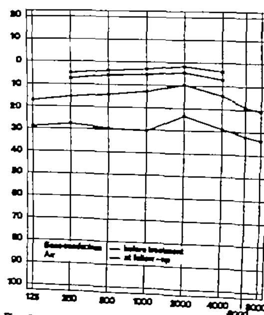


Fig. 2. The mean audiogram of the total material before treatment (161 ears) and at follow-up (238 ears)

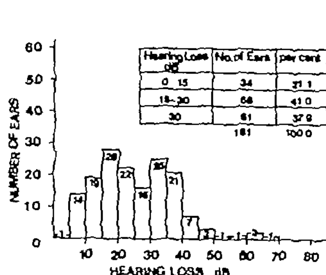


Fig 3 Air conduction threshold at speech frequencies (average of the frequencies 500, *1000 and 2000 Hz) in* the total material on admission for treatment.

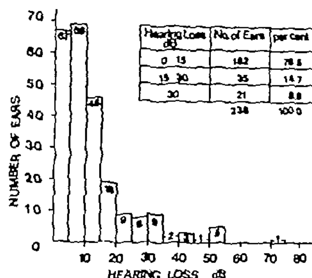


Fig 4 Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) in the total *material at follow up*

5 0 dB (S D 7 2) and the mean air bone gap 7 3 dB Compared with the pre-treatment values the air conduction threshold had improved by 15 3 dB (the difference was statistically highly significant $p<0\ 001$) the bone conduction threshold had deteriorated by 2.0 dB (the difference was not statistically significant) and the mean air bone gap had diminished by 17 3 dB (Fig 2) The youngest patient undergoing audiometric examination at the follow up study was 3 years and the mean age was 9 8 years.

When first seen the air conduction threshold at speech frequencies exceeded 30 dB in 61 ears (37 9 %) (Fig 3) At the follow up examination the air conduction threshold at speech frequencies exceeded 30 dB in 21 ears (8 8 %) (Fig 4)

At the follow up examination 4 patients were found to have an air conduction threshold exceeding 30 dB at speech frequencies in both ears. Two of these patients had a perceptive *hearing defect* exceeding 30 dB in both ears, one had an unexplicable conductive hearing defect in both ears and the fourth had a bilateral adhesive otitis media resulting from neglected *therapy*

The correlation of the final hearing result with the distance from hospital is presented in Table XII The patients who lived at a distance of less than 100 *km from the hospital had at the* follow up examination an air conduction *threshold that at speech frequencies was better* by 2.8 dB than those living at a distance exceeding 100 km (the difference was not statistically significant) while the air conduction threshold at speech frequencies on admission had been practically the same in both groups.

In 2 ears the bone conduction threshold at the follow up examination was found to have

Table XII *Influence of distance from hospital on the hearing result. The mean air conduction threshold at speech frequencies (average of the frequencies 500, 1000 and 2000 Hz) on admission for treatment and at follow-up in patients living at a distance of less than 100 km from hospital, compared with the corresponding values for those living at a distance of over 100 km from hospital.*

Distance	Threshold on admission (dB)	No of ears	Threshold at follow-up (dB)	No. of ears	*Improvement* in threshold *(dB)*
under 100 km	27 2	67	10 8	116	16.4
over 100 km	27 9	94	13 6	122	14.3

deteriorated during treatment. In one of these ears, mastoidectomy had been carried out for prolonged discharge and radiographic mastoiditis. At the follow-up examination the bone conduction threshold was found to have fallen to the 20 dB level at 4000 Hz. In addition a 70 dB high-tone loss at 6000 and 8000 Hz was observed in the air conduction thresholds. In the other of these ears, tympanotomy had been made and an anomalous middle ear been diagnosed, but no reconstruction could be carried out. At the follow-up examination, the bone conduction threshold was found to be at the 20 dB level at all frequencies, while air conduction threshold was at the 70—80 dB level.

4.2.2 The tympanostomy group

4.2.2.1 Total group

Of all patients treated with tympanostomy the hearing of 82 patients, a total of 134 ears, could be measured by audiometry on admission. Ears in which a tympanal anomaly had been diagnosed or was suspected, ears with a perceptive hearing defect and ears that had been operated on during the follow-up period were excluded from the statistical treatment. The mean values and standard deviations of the air and bone conduction thresholds of the different frequencies are presented in Table XIII The

Table XIII *Hearing level on admission of 82 patients treated with tympanostomy The air conduction figures are mean values for 134 ears, bone conduction figures for 102 ears.*

Frequency (Hz)	Hearing level (dB)			
	Air conduction		Bone conduction	
	Mean	S.D	Mean	S.D
125	28.4	11 1		
250	27.0	11.6	4.0	4 4
500	29.0	12.1	2.7	5.3
1000	29 7	13.1	2.7	5.8
2000	22.5	11.0	1.2	5 4
4000	28.5	13.7	2.8	5.2
6000	31 9	13.6		
8000	33.5	14.0		

Table XIV *Hearing level 1 month after tube insertion in 94 patients treated with tympanostomy. The air conduction figures are mean values for 147 ears, bone conduction figures for 8 ears.*

Frequency (Hz)	Hearing level (dB)			
	Air conduction		Bone conduction	
	Mean	S.D	Mean	S.D
125	14.9	8.0		
250	11 9	8.5	5.0	5.3
500	11.3	9 1	5.0	5.3
1000	10.4	9 4	1 9	7.5
2000	6.7	8.1	—1.9	4.6
4000	10.5	9.3	0.0	3.8
6000	14.5	11.6		
8000	16.8	12.8		

mean air conduction threshold at speech frequencies was 27 1 dB (S.D 12.5) the corresponding mean bone conduction threshold 2.6 dB (S.D 5.5) and the mean air-bone gap 24.5 dB. The youngest patient examined with audiometry was 4 years old, the mean age was 8 6 years.

An audiometric hearing test had been carried out on average 1 month after the tube insertion on 94 patients representing 147 ears (Table XIV) The mean air conduction threshold of the speech frequencies was 9.5 dB (S.D 8.8) the corresponding bone conduction threshold 1 7 dB (S.D 6.0) and the mean air bone gap 7.8 dB The youngest patient tested with audiometry was 4 years old, and the mean age was 8.7 years. Compared with the preoperative values, the air conduction threshold had improved by 17 6 dB (the difference was statistically highly significant, $p<0.001$) the bone conduction threshold by 0 9 dB (the difference was not statistically significant) and the air bone gap had diminished by 16.7 dB.

In connection with the follow-up examination, on average 2 years 8 months after the insertion of the tube a hearing test was carried out on 124 patients representing 202 ears (Table XV) The mean air conduction threshold at speech frequencies was 11.3 dB (S.D 9 2) the corresponding mean bone conduction value 3.2 dB (S.D 3.9) and the mean air-bone gap 8.1

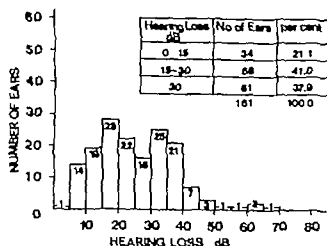


Fig 3. Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) in the total material on admission for treatment.

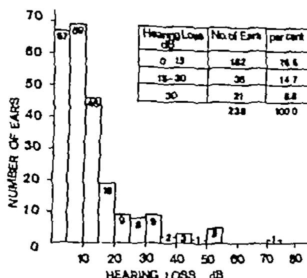


Fig 4 Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) in the total material at follow-up

5 0 dB (S D 7 2) and the mean air-bone gap 7.3 dB Compared with the *pre-treatment values* the air conduction threshold had improved by 15 3 dB (the *difference was statistically highly* significant $p < 0\ 001$) the bone conduction threshold had deteriorated by 2.0 dB (the difference was not statistically significant) and the mean air bone gap had diminished by 17.3 dB (Fig 2) The youngest patient undergoing audiometric examination at the follow up study was 3 years and the mean age was 9 8 years

When first seen the air conduction threshold at speech frequencies exceeded 30 dB in 61 ears (37 9 %) (Fig 3) At the follow up examination the air conduction threshold at speech frequencies exceeded 30 dB in 21 ears (8.8 %) (Fig 4)

At the follow up examination 4 patients were found to have an air conduction threshold exceeding 30 dB at speech frequencies in both ears. Two of these patients had a perceptive hearing defect exceeding 30 dB in both ears one had an unexplicable conductive hearing defect in both ears, and the fourth had a bilateral adhesive otitis media resulting from neglected therapy

The correlation of the final hearing result with the distance from hospital is presented in Table XII The patients who lived at a *distance of* less than 100 km from the hospital had at the follow up examination an air conduction threshold that at speech frequencies was better by 2 8 dB than those living at a distance exceeding 100 km (the difference was not statistically significant) while the air conduction threshold at speech frequencies on admission had been practically the same in both groups.

In 2 ears the bone conduction threshold at the follow up examination was found to have

Table XII *Influence of distance from hospital on the hearing result. The mean air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) on admission for treatment and at follow-up in patients living at a distance of less than 100 km from hospital, compared with the corresponding values for those living at a distance of over 100 km from hospital.*

Distance	Threshold on admission (dB)	No. of ears	Threshold at follow up (dB)	No. of ears	Improvement in threshold (dB)
under *100* km	*27.2*	67	*10 8*	*116*	16.4
over 100 km	27 9	94	13.6	122	14.3

deteriorated during treatment. In one of these ears, mastoidectomy had been carried out for prolonged discharge and radiographic mastoiditis. At the follow-up examination the bone conduction threshold was found to have fallen to the 20 dB level at 4000 Hz. In addition, a 70 dB high-tone loss at 6000 and 8000 Hz was observed in the air conduction thresholds. In the other of these ears, tympanotomy had been made and an anomalous middle ear been diagnosed, but no reconstruction could be carried out. At the follow-up examination, the bone conduction threshold was found to be at the 20 dB level at all frequencies, while air conduction threshold was at the 70—80 dB level.

.2.2. *The tympanotomy group*

.2.2.1 Total group

Of all patients treated with tympanotomy the hearing of 82 patients, a total of 134 ears, could be measured by audiometry on admission. Ears in which a tympanal anomaly had been diagnosed or was suspected, ears with a perceptive hearing defect and ears that had been operated on during the follow up period were excluded from the statistical treatment. The mean values and standard deviations of the air and bone conduction thresholds of the different frequencies are presented in Table XIII. The

Table XIII. *Hearing level on admission of 82 patients treated with tympanotomy. The air conduction figures are mean values for 134 ears, bone conduction figures for 102 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	28.4	11.1		
250	27.0	11.6	4.0	4.4
500	29.0	12.1	3.7	5.3
1000	29.7	13.1	2.7	5.8
2000	22.5	11.0	1.2	5.4
4000	28.5	13.7	2.8	5.2
6000	31.9	13.6		
8000	33.5	14.0		

Table XIV. *Hearing level 1 month after tube insertion in 94 patients treated with tympanotomy. The air conduction figures are mean values for 147 ears, bone conduction figures for 8 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	14.9	8.0		
250	11.9	8.5	5.0	5.3
500	11.2	9.1	5.0	5.3
1000	10.4	9.4	1.9	7.5
2000	6.7	8.1	−1.9	4.6
4000	10.5	9.3	0.0	3.8
6000	14.5	11.6		
8000	16.8	12.8		

mean air conduction threshold at speech frequencies was 27.1 dB (S.D 12.5) the corresponding mean bone conduction threshold 2.6 dB (S.D 5.5) and the mean air bone gap 24.5 dB. The youngest patient examined with audiometry was 4 years old, the mean age was 8.6 years.

An audiometric hearing test had been carried out on average 1 month after the tube insertion on 94 patients representing 147 ears (Table XIV). The mean air conduction threshold of the speech frequencies was 9.5 dB (S.D 8.8) the corresponding bone conduction threshold 1.7 dB (S.D 6.0) and the mean air-bone gap 7.8 dB. The youngest patient tested with audiometry was 4 years old, and the mean age was 8.7 years. Compared with the preoperative values, the air conduction threshold had improved by 17.6 dB (the difference was statistically highly significant, $p < 0.001$) the bone conduction threshold by 0.9 dB (the difference was not statistically significant) and the air-bone gap had diminished by 16.7 dB.

In connection with the follow-up examination on average 2 years 8 months after the insertion of the tube a hearing test was carried out on 124 patients representing 202 ears (Table XV). The mean air conduction threshold at speech frequencies was 11.3 dB (S.D 9.2) the corresponding mean bone conduction value 3.2 dB (S.D 3.9) and the mean air bone gap 8.1

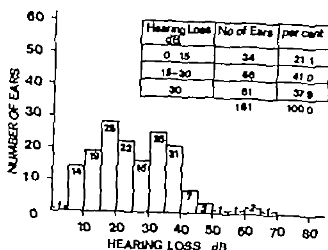


Fig 3 Air conduction threshold at speech frequencies (average of the *frequencies 500 1000 and 2000 Hz) in* the total material on admission for treatment.

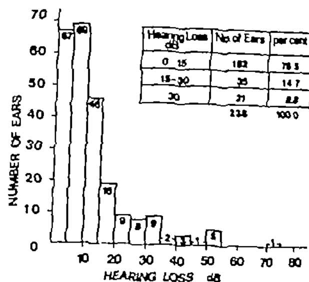


Fig 4 Air conduction threshold at speech frequencies (average *of the frequencies 500 1000 and 2000 Hz) in* the total material at follow-up

5 0 dB (S D 7 2) and the mean air bone gap 7.3 dB Compared with the pre-treatment values the air conduction threshold had improved by 15 3 dB (the difference was statistically highly significant $p < 0\ 001$) the bone conduction threshold had deteriorated by 2.0 dB (the difference was not statistically significant) and the mean air bone gap had diminished by 17 3 dB (Fig 2) The youngest patient undergoing audiometric examination at the follow up study was 3 years and the mean age was 9 8 years

When first seen the air conduction threshold at speech frequencies exceeded 30 dB in 61 ears (37 9 %) (Fig 3) At the follow up examination the air conduction threshold at speech frequencies exceeded 30 dB in 21 ears (8 8 %) (Fig 4)

At the follow up examination 4 patients were found to have an air conduction threshold exceeding 30 dB at speech frequencies in both ears. Two of these patients had a perceptive hearing defect exceeding 30 dB in both ears one had an unexplicable conductive hearing defect in both ears, and the fourth had a bilateral adhesive otitis media resulting from neglected therapy

The correlation of the final hearing result with the distance from hospital is presented in Table XII The patients who lived at a distance of less than 100 km from the hospital had at the follow up examination an air conduction threshold that at speech frequencies was better by 2.8 dB than those living at a distance exceeding 100 km (the difference was not statistically significant) while the air conduction threshold at speech frequencies on admission had been practically the same in both groups.

In 2 ears the bone conduction threshold at the follow up examination was found to have

Table XII *Influence of distance from hospital on the hearing result. The mean air conduction threshold at speech frequencies (average of the frequencies 500, 1000 and 2000 Hz) on admission for treatment and at follow-up in patients living at a distance of less than 100 km from hospital, compared with the corresponding values for those living at a distance of over 100 km from hospital.*

Distance	Threshold on admission (dB)	No. of ears	Threshold at follow-up (dB)	No. of ears	Improvement in threshold (dB)
under 100 km	27 2	67	10 8	116	16.4
over 100 km	27 9	94	13.6	122	14.3

Table XVII. Hearing level 1 month after tube insertion in 64 patients treated with tympanostomy whose disease had healed by the time of the follow-up. The air conduction figures are mean values for 94 ears, bone conduction figures for 4 ears.

Frequency	Hearing level (dB)			
	Air conduction		Bone conduction	
(Hz)	Mean	S.D	Mean	S.D
125	13.5	5.5		
250	9.9	5.5	2.5	2.9
500	9.3	6.2	−2.5	6.4
1000	8.7	6.6	−3.7	4.8
2000	5.5	5.6	−5.0	0.0
4000	9.4	6.7	−2.5	2.9
6000	12.3	9.0		
8000	14.5	10.9		

conduction threshold at speech frequencies was 8 dB (S.D 5.8) for the whole group. The bone conduction threshold was measured only on 4 patients. The youngest patient tested with audiometry was 4 years old, and the mean age was 9.4 years. The air conduction threshold had improved by 18.0 dB from the preoperative value (the difference was statistically highly significant, p <0.001).

At the follow-up examination, the audiometric test was carried out on 87 patients and a total of 143 ears (Table XVIII). The mean air conduction threshold at speech frequencies was .6 dB (S.D 6.9); the corresponding bone

Table XVIII. Hearing level at follow-up of 87 patients treated with tympanostomy whose disease had healed. The air conduction figures are mean values for 143 ears, bone conduction figures for 14 ears.

Frequency	Hearing level (dB)			
	Air conduction		Bone conduction	
(Hz)	Mean	S.D	Mean	S.D.
125	14.5	6.9		
250	12.3	6.5	5.7	2.7
500	11.0	6.7	3.9	2.9
1000	10.0	7.0	2.1	3.8
2000	7.8	6.5	1.8	4.8
4000	11.3	7.9	5.4	5.7
6000	15.8	9.1		
8000	17.4	9.8		

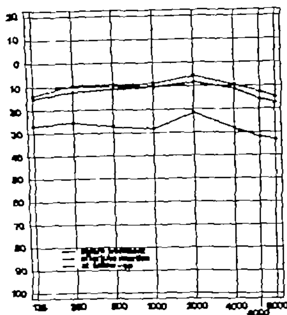


Fig. 6. Mean audiogram (air conduction) of ears treated with tympanostomy tubes and found healed at follow-up on admission (68 ears), 1 month after tube insertion (94 ears) and at follow-up (143 ears).

conduction value was 2.6 dB (S.D 3.9) and the mean air-bone gap 7.0 dB. The youngest of the patients tested was 3 years old, and the mean age was 9.6 years. The mean air conduction threshold had improved by 16.2 dB from the preoperative value (the difference was statistically highly significant, p<0.001) and deteriorated by 1.8 dB from the immediate post operative value (the difference was not statistically significant) (Fig. 6). The mean bone

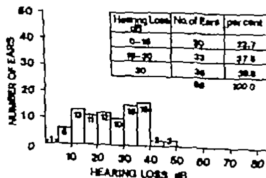


Fig. 7. Air conduction threshold at speech frequencies (average of the frequencies 500, 1000 and 2000 Hz) of ears treated with tympanostomy tubes and found healed at follow-up, on admission.

Table XV *Hearing level at follow-up of 124 patients treated with tympanostomy The air conduction figures are mean values for 202 ears, bone conduction figures for 26 ears*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S D
125	16 6	9 1		
250	14.3	8.6	6.7	2.8
500	13 0	9.5	4 6	2.8
1000	11.8	9.2	3.5	3 7
2000	9 1	8.6	1.5	4 4
4000	12 9	10.0	5 6	5 2
6000	17 6	11.2		
8000	19.3	12.6		

dB The youngest of the patients tested was 3 years old, and the mean age was 9 7 years The air conduction threshold had improved by 15 6 dB from the preoperative value (the difference was statistically highly significant $p<0$ 001) but deteriorated by 1 8 dB from the immediate postoperative value (the difference was not statistically significant) (Fig 5) The bone

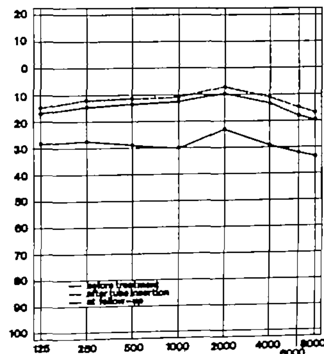


Fig 5. Mean audiogram (air conduction) of the ears treated with tympanostomy tubes on admission (134 ears) 1 month after tube insertion (147 ears) and at follow-up (202 ears)

conduction threshold had deteriorated by 0 6 dB from the preoperative value (the difference was not statistically significant) and by 1.5 dB from the immediate postoperative value (the difference was not statistically significant) The air bone gap had diminished by 16 4 dB from the preoperative value but increased by 0.3 dB from the postoperative value.

4.2.2 2. Chronic secretory otitis media healed at the follow up examination

This group comprises the patients in whom chronic secretory otitis media was found to have healed during the follow up period, the tubes had been extruded and the eardrums were intact.

On admission, the audiometric test could be carried out on 56 patients, and a total of 88 ears (Table XVI) The mean air conduction threshold at speech frequencies was 25 8 dB (S D 12.1) the corresponding mean bone conduction threshold was 2 0 dB (S D 5 9) and the mean air bone gap 23 8 dB The youngest of the patients tested was 4 years old, and the mean age was 9 2 years

About 1 month after the insertion of the tubes the hearing of 64 patients, representing 94 ears, had been tested (Table XVII) The mean air

Table XVI *Hearing level on admission of 56 patients treated with tympanostomy whose disease had healed by the time of the follow-up. The air conduction figures are mean values for 88 ears, bone conduction figures for 70 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S D	Bone conduction Mean	S D
125	26.8	10 6		
250	25 2	10.8	3.3	4 6
500	27.5	11 4	2.9	5.3
1000	28.1	12.9	2.2	6.0
2000	21 6	10 8	0.8	5.8
4000	28.0	14 7	2.4	5.0
6000	31 7	13 7		
8000	32.8	15 0		

Table XVII. *Hearing level 1 month after tube insertion in 64 patients treated with tympanostomy whose disease had healed by the time of the follow-up. The air conduction figures are mean values for 94 ears, bone conduction figures for 4 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	13.5	5.5		
250	9.9	5.5	2.5	2.9
500	9.3	6.2	−2.5	6.4
1000	8.7	6.6	−3.7	4.8
2000	5.5	5.6	−5.0	0.0
4000	9.4	6.7	−2.5	2.9
6000	12.3	9.0		
8000	14.5	10.9		

conduction threshold at speech frequencies was 7.8 dB (S.D 5.8) for the whole group. The bone conduction threshold was measured only on 4 patients. The youngest patient tested with audiometry was 4 years old, and the mean age was 9.4 years. The air conduction threshold had improved by 18.0 dB from the preoperative value (the difference was statistically highly significant, $p<0.001$)

At the follow-up examination, the audiometric test was carried out on 87 patients and a total of 143 ears (Table XVIII). The mean air conduction threshold at speech frequencies was 9.6 dB (S.D 6.9) the corresponding bone

Table XVIII. *Hearing level at follow-up of 87 patients treated with tympanostomy whose disease had healed. The air conduction figures are mean values for 143 ears, bone conduction figures for 14 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D.
125	14.5	6.9		
250	12.3	6.5	5.7	2.7
500	11.0	6.7	3.9	2.9
1000	10.0	7.0	2.1	3.8
2000	7.8	6.5	1.8	4.8
4000	11.3	7.9	5.4	5.7
6000	15.8	9.1		
8000	17.4	9.8		

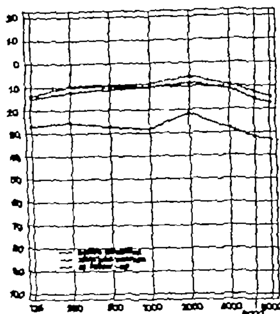


Fig. 6. Mean audiogram (air conduction) of ears treated with tympanostomy tubes and found healed at follow-up on admission (84 ears), 1 month after tube insertion (94 ears) and at follow-up (143 ears)

conduction value was 2.6 dB (S.D 3.9) and the mean air bone gap 7.0 dB. The youngest of the patients tested was 3 years old, and the mean age was 9.6 years. The mean air conduction threshold had improved by 16.2 dB from the preoperative value (the difference was statistically highly significant, $p<0.001$) and deteriorated by 1.8 dB from the immediate postoperative value (the difference was not statistically significant) (Fig. 6). The mean bone

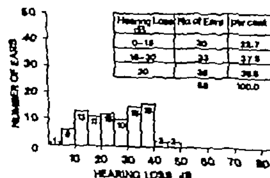


Fig. 7. Air conduction threshold at speech frequencies (average of the frequencies 500, 1000 and 2000 Hz) of ears treated with tympanostomy tubes and found healed at follow-up, on admission.

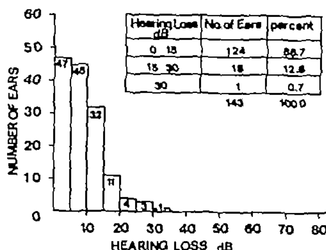


Fig 8. Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) of *ears treated with tympanostomy tubes and found healed at follow up at the follow up examination.*

conduction threshold had deteriorated by 0 6 dB from the preoperative value (the difference was *not* statistically significant) The mean air bone *gap* had *diminished* by 16 8 dB from the preoperative value

On admission for treatment the air conduction threshold at speech frequencies exceeded 30 dB on 35 ears (39 8 %) (Fig 7) but at the follow up examination in only one (0 7 %) (Fig 6)

4 2.2.3 Tubes in position at the follow up examination

On admission the hearing of 15 patients and a total of 28 ears had been tested The mean air conduction threshold at speech frequencies in the whole group was 29 6 *dB (S D 12.4)* the *corresponding mean bone conduction threshold* 3 2 dB (S D 4 6) and the mean air bone gap 26 4 dB The youngest of the patients tested was 4 years old, and the mean age was 7 1 years

About 1 month after the insertion of the tubes a hearing test was made on 19 patients representing 34 ears. The mean air conduction threshold at speech frequencies was *10 0 dB (S D 7 2) it had improved* by 19 6 dB from the preoperative value (the difference was statistically highly significant p <0 001) The youngest of the patients tested was 4 years old and the mean age was 7 3 years.

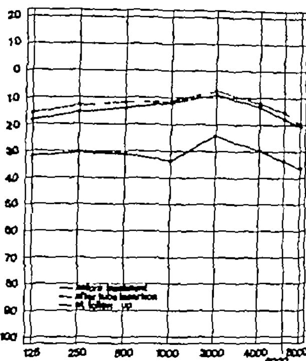


Fig 9 Mean audiogram (air conduction) of ears *treated with tympanostomy tubes and with tubes in* position at follow-up on admission (28 ears) 1 month after tube insertion (34 ears) and at follow-up (29 ears)

At the follow up examination the audiometric hearing test was carried out on 16 patients and a total of 29 ears. The mean air conduction *threshold at speech frequencies* was *11.5 dB (S D 9 7)* The improvement from the preoperative value was 18.1 dB (the difference was statistically highly significant p <0 001) and deterioration from the immediate postoperative value was 1.5 dB (the difference was not statistically significant) (Fig 9) The youngest of the patients tested was 3 years *old, and the mean age* was 9 2 years.

4 2.2.4 The cleft palate patients

The tympanostomy group contained *10 operated* cleft palate *patients. On admission the hearing of* 3 patients and a total of 6 ears had been tested The mean air conduction threshold at speech frequencies was 36 1 dB (S D 9 2) the corresponding bone conduction threshold 2.9 dB (S D 3 3) and the mean air-bone gap 33.2 dB

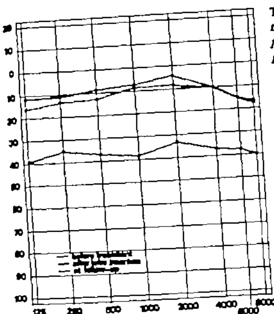


Fig. 10. Mean audiogram (air conduction) of the cleft palate patients treated with tympanostomy tubes, on admission (6 ears) 1 month after tube insertion (6 ears) and at follow-up (10 ears)

The youngest patient tested was 7 years old, and the mean age was 7 7 years.

At the follow-up examination the audiometric hearing test was carried out on 5 patients representing 10 ears. Three patients (6 ears) still had the tubes in position The mean air conduction threshold at speech frequencies was 6.7 dB (S.D 5.2) Compared with the preoperative value the mean air conduction threshold had improved by 29 4 dB (the difference was statistically highly significant, $p<0.001$) (Fig. 10) The youngest of the patients tested was 4 years old and the mean age was 9 2 years.

4.2.3. *Patients treated without tympanostomy*

On admission, the hearing of 10 patients representing 18 ears could be measured by audiometry (Table XIX). The mean air conduction threshold at speech frequencies was 22.8 dB (S.D 12.1) the corresponding bone conduction threshold −2.0 dB (S.D 4.2) and

Table XIX. *Hearing level on admission of 10 patients treated without tympanostomy. The air conduction figures are mean values for 18 ears, bone conduction figures for 11 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D	Bone conduction Mean	S.D
125	25.3	10.1		
250	23.1	11.3	2.7	4 7
500	25.8	9 6	−0.5	2.7
1000	24.7	13.1	−1.8	4.0
2000	17.8	11.7	−3.6	5.0
4000	23.9	13.9	−0.9	5.4
6000	22.9	11.7		
8000	28.9	10.6		

Table XX. *Hearing level at follow-up 16 patients treated without tympanostomy. The air conduction figures are mean values for 27 ears, bone conduction figures for 7 ears.*

Frequency (Hz)	Hearing level (dB) Air conduction Mean	S.D.	Bone conduction Mean	S.D
125	17.2	14.6		
250	16.1	15.1	2.1	3.9
500	14.8	14.4	2.9	3.9
1000	13.3	14.0	3.6	5.6
2000	8.1	11.4	−0.7	3.4
4000	14.6	15.1	6.4	3.8
6000	18.5	13.0		
8000	18.9	13.2		

the mean air-bone gap 24.8 dB The youngest patient tested by audiometry was 4 years old, and the mean age of the group was 7 9 years.

At the follow-up examination, on average 4 years 7 months later the audiometric hearing test was carried out on 16 patients representing 27 ears (Table XX) The mean air conduction threshold at speech frequencies was 12.1 dB (S.D 13.5) the corresponding bone conduction threshold 1.9 dB (S.D 4 6) and the mean air bone gap 10.2 dB. The youngest of the patients tested was 5 years old, and the mean age of the group was 10.6 years. The air conduction threshold at speech frequencies had improved by

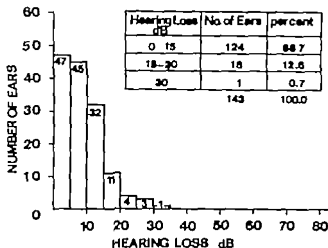


Fig 8 Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) of ears treated with tympanostomy tubes and found healed at follow up at the follow up examination.

conduction threshold had deteriorated by 0 6 dB from the preoperative value (the difference was not statistically significant) The mean air bone gap had diminished by 16 8 dB from the preoperative value

On admission for treatment the air conduction threshold at speech frequencies exceeded 30 dB on 35 ears (39 8 %) (Fig 7) but at the follow up examination in only one (0 7 %) (Fig 8)

4.2.2.3 Tubes in position at the follow up examination

On admission the hearing of 15 patients, and a total of 28 ears had been tested The mean air conduction threshold at speech frequencies in the whole group was 29 6 dB (S D 12 4) the corresponding mean bone conduction threshold 3 2 dB (S D 4 6) and the mean air bone gap 26 4 dB The youngest of the patients tested was 4 years old and the mean age was 7 1 years.

About 1 month after the insertion of the tubes a hearing test was made on 19 patients representing 34 ears. The mean air conduction threshold at speech frequencies was 10 0 dB (S D 7 2) it had improved by 19 6 dB from the preoperative value (the difference was statistically highly significant, $p < 0.001$) The youngest of the patients tested was 4 years old and the mean age was 7 3 years

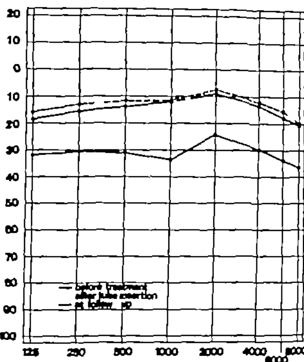
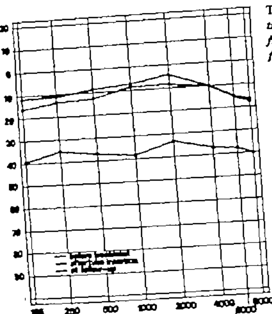


Fig 9 Mean audiogram (air conduction) of ears treated with tympanostomy tubes and with tubes in position at follow up on admission (28 ears) 1 month after tube insertion (34 ears) and at follow-up (29 ears)

At the follow up examination the audiometric hearing test was carried out on 16 patients and a total of 29 ears The mean air conduction threshold at speech frequencies was 11.5 dB (S.D 9 7) The improvement from the preoperative value was 18 1 dB (the difference was statistically highly significant, $p < 0.001$) and deterioration from the immediate postoperative value was 1.5 dB (the difference was not statistically significant) (Fig 9) The youngest of the patients tested was 3 years old and the mean age was 9 2 years.

4.2.2.4 The cleft palate patients

The tympanostomy group contained 10 operated cleft palate patients On admission the hearing of 3 patients and a total of 6 ears had been tested The mean air conduction threshold at speech frequencies was 36 1 dB (S D 9 2) the corresponding bone conduction threshold 2.9 dB (S D 3.3) and the mean air bone gap 33 2 dB.



[Fi]g. 10. Mean audiogram (air conduction) of the cleft [pa]late patients treated with tympanostomy tubes, on [ad]mission (6 ears) 1 month after tube insertion (6 [ea]rs), and at follow-up (10 ears)

The youngest patient tested was 7 years old, and the mean age was 7 7 years.

At the follow-up examination the audiometric hearing test was carried out on 5 patients representing 10 ears. Three patients (6 ears) still had the tubes in position. The mean air conduction threshold at speech frequencies was 6.7 dB (S D 5.2) Compared with the preoperative value the mean air conduction threshold had improved by 29 4 dB (the difference was statistically highly significant, $p<0.001$) (Fig. 10) The youngest of the patients tested was 4 years old and the mean age was 9.2 years.

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250	16.1	15.1	2.1	3.9
500	14.8	14 4	2.9	3.9
1000	13.3	14.0	3.6	5.6
2000	8.1	11.4	—0.7	3 4
4000	14 6	15 1	6.4	3.8
6000	18.5	13.0		
8000	18.9	13.2		

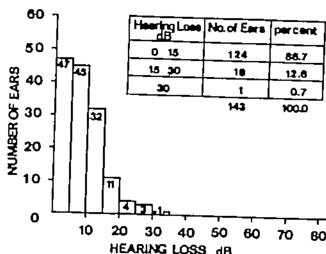


Fig 8. Air conduction threshold at speech frequencies (average of the frequencies 500 1000 and 2000 Hz) of ears treated with tympanostomy tubes and found healed at follow-up at the follow up examination.

conduction threshold had deteriorated by 0 6 dB from the preoperative value (the difference was not statistically significant) The mean air bone gap had diminished by 16 8 dB from the preoperative value

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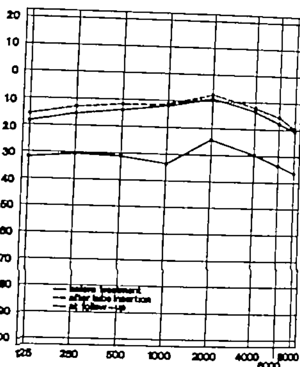


Fig 9 Mean audiogram (air conduction) of ears treated with tympanostomy tubes and with tubes in position at follow up on admission (28 ears) 1 month after tube insertion (34 ears) and at follow up (29 ears)

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4 2.2.4 The cleft palate patients

The tympanostomy group contained 10 operated cleft palate patients On admission the hearing of 3 patients and a total of 6 ears had been tested. The mean air conduction threshold at speech frequencies was 36 1 dB (S.D 9 2) the corresponding bone conduction threshold 2.9 dB (S D 3.3) and the mean air-bone gap 33 2 dB

5. DISCUSSION

According to Lumio (1957) Juselius (1958) and Watson (1969) chronic secretory otitis media is the most common cause of impaired hearing in childhood. Watson states that this disease accounted for 81 % of the impaired hearing among 5-year olds but 0 % among 13-year olds. According to several earlier studies the incidence of chronic secretory otitis media is highest among children aged 4—8 years (Hoople, 1950· Armstrong, 1957 Lemon, 1962; Kersley & Wickham, 1966; Hussl 1973a) The present material differs from the above in that the group of children under 1 year was numerically the greatest. The second largest age group was 7—8 years, the age at which children start school and are subjected to systematic hearing tests. These findings support Hussl's (1973a) idea that chronic secretory otitis media also occurs among the younger age groups but due to its slight symptoms is less frequently diagnosed. The diagnosis in an uncooperative child is successful only if the routine ear examination is made with Siegle s pneumatic speculum and if diagnostic paracentesis is made in suspected cases (Hussl 1973a)

The studies of recent years seem to have conclusively shown that chronic secretory otitis media is a result of a postinflammatory increase of the mucus-producing elements of the middle ear and the accompanying dysfunction of the Eustachian tube (Bendek, 1963 Friedman, 1963 Sadé, 1966 Lim & Hussl, 1969· Tos & Bak Pedersen, 1972, 1973 Bak Pedersen & Tos, 1971 1973 Bernstein et al. 1973, Palva et al. 1974a, 1974b) On the basis of the above studies it seems plausible that omission of paracentesis in acute otitis media is contributory to the increase of chronic secretory otitis media in the era of antibiotics (Suehs, 1956· Armstrong, 1957 Friedman, 1963· Palva & Karma, 1973 Palva et al. 1974a, 1974b) In the present material of 181 patients, the annual number of those seeking treatment has grown continuously This, however does not directly indicate any true increase in chronic secretory otitis media, for in earlier years the majority of patients were treated at outpatient clinics by repeated paracentesis, and these patients are not at all covered by the present study

In the present material the sex distribution in chronic secretory otitis media was similar to that reported by Eagle (1946) Solow (1958) and Draper (1967) — c 60 % boys and 40 % girls. It is difficult to pinpoint the reason for the overrepresentation of boys. In Solow's opinion the distribution is the same as that of allergy before puberty This does not hold good concerning the present material where respiratory allergy was diagnosed in only 5 patients (2.8 %)· admittedly eosinophils were not sought systematically The share of allergy in this material was markedly smaller than in Jordan s (1952) material, but agreed with the findings reported by Lemon (1962) and Kersley & Wickham (1966)

The adenoids, the infections of the nose and nasal sinuses, and changes in the tubal orifice have been found to play a part in the etiology of chronic secretory otitis media. Furthermore, cleft palate patients have been found to have a remarkably high disposition to the disease (Stool & Randall, 1967) In the present series, 27 patients (14.9 %) were found to have sinusitis, 8 patients (4 4 %) a pathological nasopharyngeal status, and 10 patients (5.5 %) an operated or unoperated cleft palate on admission for treatment. Very large-sized adenoids were seen in 37 patients (20 4 %). Dawes (1970) and Maw son & Fagan (1972) are of the opinion that there is no evidence to support "adenoidectomy"

10 7 dB (the difference was statistically highly significant p<0 001) The bone conduction threshold had deteriorated by 3 9 dB (the difference was statistically not significant) (Fig 11) and the mean air bone gap had diminished by 14 6 dB

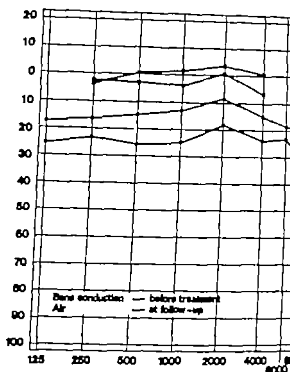


Fig 11 Mean audiogram of the conservatively treat
ears on admission (18 ears) and at follow-up (27 ear

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as a primary form of treatment but the present author finds that adenotomy must be made and the infections of the nose and nasopharynx treated before tube theraby is instituted Mawson & Fagan first carried out myringotomy and aspiration on their patients and if aspiration was still positive a second time they inserted the tubes In the present material myringotomy and aspiration were carried out first and the next step if required was adenotomy After this the patients were given a weekly check up and, if necessary paracentesis and aspiration were performed Only if the disease failed to heal with this treatment were tubes inserted The mean interval from the diagnosis of chronic secretory otitis media to the insertion of tympanostomy tubes was 8.5 months The interval must be considered too long· on the other hand a number of patients were symptom free for several months during this interval. The best policy seems to be if the paracentesis made weekly after the adenotomy is positive on 2—3 occasions to insert the tympanostomy tubes This of course does not apply to cleft palates and other special cases in which the insertion of the tubes is indicated as soon as the disease has been diagnosed.

The present series included 2 patients whose tubal orifices were badly strictured after an earlier adenotomy In both patients the tympanostomy tube therapy lasted more than 24 months and after every extrusion of the tubes the disease recurred. To avoid this adenotomy should always be carried out under general anaesthesia and under visual control taking special care not to damage the Eustachian tubes.

According to Turner (1967) the mean period during which a polyethylene tube remained ventilating was 10 9 weeks against 24 weeks for silastic and teflon tubes. In the material published by Mawson & Fagan (1972) the mean survival of Shephard's teflon tubes was 6 6 months In the present study most patients were fitted with polyethylene tubes of our own make only a few having ready-made silastic tubes. The mean survival of 511 tympanostomy tubes was 7 0 months. As a rule, tympanostomy tubes should not be removed but allowed to be spontaneously extruded.

It used to be a common belief that the middle ear effusion in chronic secretory otitis media was sterile (Jordan 1949 Ivstamm 1954 Tönder & Gundersen 1971) In the present material, 322 bacterial samples (198 ears) were collected in connection with the insertion of the tube and 71 (22 %) of them were positive. The most common bacteria were Hemophilus influenzae, Staphylococcus aureus and Staphylococcus albus Bernstein & Hayes (1971) reported similar findings on their material. The cause of the bacteriological sterility is apparently not so much the poor culture techniques or viral etiology as the preceding antibiotic therapy and the bactericidal and bacteriostatic effect of the middle ear effusion (Siirala & Lahikainen, 1952) deriving from the IgA secreted by the middle ear mucosa (Bernstein et al 1972) According to Siirala & Lahikainen children's middle ear effusion had no effect against Hemophilus influenzae. A middle ear infection in the course of tympanostomy tube therapy has generally been considered a minor problem (Hussl 1973b) but in the present material discharge occurred during tube therapy in 41 % of the ears and if Hemophilus influenzae grew in the bacterial sample taken in connection with tube insertion, there was discharge in 79 % Mastoidectomy had to be carried out on 15 ears for persistent discharge and radiographic mastoiditis while the others healed with conservative therapy This susceptibility to infection is probably partly due to poor social conditions and the instability of the climate.

According to Politzer (1878) and Zechner (1969) chronic secretory otitis media if left untreated leads to chronic adhesive otitis media. In the present series, both eardrums of one patient were found to be adhesive at the follow up examination. This patient treated without tympanostomy had had purulent discharge from both ears. Treatment had been neglected and the result was bilateral adhesive otitis and a poor hearing result. This case supports the assumption by Ojala (1953) concerning the etiology of adhesive otitis

According to Ojala, recurrent infections exceeding a given minimum and, additionally a deteriorated drainage are necessary before adhesive otitis can develop. Adhesive otitis media was not seen in any of the ears treated with *tympanostomy although in 2 ears (0.7 %) a small area of the drum adhered to the* promontorium. In these ears, also, there had been purulent discharge that had not been treated adequately.

According to Zalin (1963) chronic secretory otitis media is an intermediate stage in the development of cholesteatoma, and Jordan (1963) reported on 11 cases in which cholesteatoma developed during the course of treatment for chronic secretory otitis media. The 165-patient series of MacKinnon (1971) contained 8 cholesteatomas. In the present material of 181 patients representing 313 ears the follow up examination disclosed 4 cholesteatomas (1.4 %) of which 2 (0.7 %) can be considered a complication of tube therapy. During the tube therapy these 2 ears showed a purulent discharge which was not treated in any way. As a result of prolonged discharge both ears developed a marginal perforation and later a cholesteatoma. One patient, during the tympanostomy tube therapy developed an attic cholesteatoma in both ears as the result of retraction of Shrapnell's membrane.

A complication more frequent than cholesteatoma in the present material was persistent perforation. At the follow-up examination, 12 perforations were recorded, and additionally myringoplasty had been carried out in one ear for persistent perforation (total 4.5 %). The number of perforations considerably exceeded that reported by MacKinnon (1971) and by Mawson & Fagan (1972). The large number of perforations in the present series was apparently a result of the high rate of discharge. On the other hand, the purpose of tympanostomy therapy is to create a persistent perforation, and hence perforation should actually not be considered a complication. Closing the perforation operatively is not meaningful as long as there is a risk of the disease recurring.

In the material of Mawson & Fagan (1972) the most common drum change after tympanostomy tube therapy was tympanosclerosis (30 %). The next most common were retraction of the drum (21 %), atelectasis (9 %) and a visible tympanostomy scar (5 %). In their material only 18 % of the drums were normal at the follow-up examination. In the present material, 44.8 % of the drums treated with tympanostomy were normal or nearly normal in the follow-up examination, 10.0 % were tympanosclerotic, 7.6 % pseudomembranous, 5.2 % scarred, 3.0 % atrophic, 2.1 % retracted, and 2.1 % adhered to the head of the stapes. The tympanostomy tubes were in position and ventilating in 22.1 %, a recurrence was seen in 3.1 %, purulent discharge from the tube in 1.7 % and complications in 7.6 %. The large proportion of normal drums in the present series compared with the above reports was probably rather a result of different criteria than better therapeutic results. In the group treated without tympanostomy 74.2 % of the drums were normal at the follow-up examination and 25.8 % were abnormal, 2 of the latter (6.5 %) were adhesive.

Hearing loss in chronic secretory otitis media varies greatly. Cohen & Sadé (1972) quoted the limit values of 0 dB and 50 dB for the threshold of the speech frequencies. In the reports of Silverstein et al. (1966), Cohen & Sadé (1972), Kilby et al. (1972), Mawson & Fagan (1972) and Hurd (1973b) the mean hearing loss at speech frequencies was 25—40 dB. In the present material the mean hearing loss at speech frequencies was 27.6 dB, ranging from 5 to 70 dB, before treatment. The 2000 Hz air conduction threshold was statistically significantly ($p < 0.01$) better than that of 250 Hz, and highly significantly ($p < 0.001$) better than those of the other frequencies. The result was the same as that reported by Harbert & Mendake (1970) and shows that 2000 Hz is the optimum frequency of the human ear in conductive defects of this type. No corresponding difference was observable in bone conduction hearing.

After the insertion of tubes the mean air conduction threshold in the present material (147 ears) was 9.5 dB. If the hearing falls to

as a primary form of treatment but the present author finds that adenotomy must be made and the infections of the nose and nasopharynx treated before tube theraby is instituted Mawson & Fagan first carried out myringotomy and aspiration on their patients and if aspiration was still positive a second time they inserted the tubes In the present material myringotomy and aspiration were carried out first and the next step if required was adenotomy After this the patients were given a weekly check up and, if necessary paracentesis and aspiration were performed Only if the disease failed to heal with this treatment were tubes inserted The mean interval from the diagnosis of chronic secretory otitis media to the insertion of tympanostomy tubes was 8.5 months. The interval must be considered too long on the other hand a number of patients were symptom free for several months during this interval The best policy seems to be if the paracentesis made weekly after the adenotomy is positive on 2—3 occasions to insert the tympanostomy tubes This of course does not apply to cleft palates and other special cases in which the insertion of the tubes is indicated as soon as the disease has been diagnosed

The present series included 2 patients whose tubal orifices were badly strictured after an earlier adenotomy In both patients the tympanostomy tube therapy lasted more than 24 months and after every extrusion of the tubes the disease recurred. To avoid this adenotomy should always be carried out under general anaesthesia and under visual control taking special care not to damage the Eustachian tubes

According to Turner (1967) the mean period during which a polyethylene tube remained ventilating was 10 9 weeks against 24 weeks for silastic and teflon tubes In the material published by Mawson & Fagan (1972) the mean survival of Shephard s teflon tubes was 6 6 months In the present study most patients were fitted with polyethylene tubes of our own make only a few having ready-made silastic tubes. The mean survival of 511 tympanostomy tubes was 7 0 months. As a rule, tympanostomy tubes should not be removed but allowed to b spontaneously extruded

It used to be a common belief that the middl ear effusion in chronic secretory otitis media wa sterile (Jordan 1949 Ivstamm 1954 Tönder & Gundersen 1971) In the present material, 32 bacterial samples (198 ears) were collected in connection with the insertion of the tube and 71 (22 %) of them were positive. The most common bacteria were Hemophilus influenzae Staphylococcus aureus and Staphylococcus albus. Bernstein & Hayes (1971) reported similar findings on their material The cause of the bacteriological sterility is apparently not so much the poor culture techniques or viral etiology as the preceding antibiotic therapy and the bactericidal and bacteriostatic effect of the middle ear effusion (Siirala & Lahikainen 1952) deriving from the IgA secreted by the middle ear mucosa (Bernstein et al 1972) According to Siirala & Lahikainen children s middle ear effusion had no effect against Hemophilus influenzae A middle ear infection in the course of tympanostomy tube therapy has generally been considered a minor problem (Hussl 1973b) but in the present material discharge occurred during tube therapy in 41 % of the ears and if Hemophilus influenzae grew in the bacterial sample taken in connection with tube insertion there was discharge in 79 % Mastoidectomy had to be carried out on 15 ears for persistent discharge and radiographic mastoiditis while the others healed with conservative therapy This susceptibility to infection is probably partly due to poor social conditions and the instability of the climate

According to Politzer (1878) and Zechner (1969) chronic secretory otitis media if left untreated leads to chronic adhesive otitis media. In the present series both eardrums of one patient were found to be adhesive at the follow up examination This patient, treated without tympanostomy had had purulent discharge from both ears. Treatment had been neglected and the result was bilateral adhesive otitis and a poor hearing result. This case supports the assumption by Ojala (1953) concerning the etiology of adhesive otitis

According to Ojala, recurrent infections exceeding a given minimum and, additionally a deteriorated drainage are necessary before adhesive otitis can develop. Adhesive otitis media was not seen in any of the ears treated with tympanostomy although in 2 ears (0.7 %) a small area of the drum adhered to the promontorium. In these ears, also, there had been purulent discharge that had not been treated adequately.

According to Zalin (1963) chronic secretory otitis media is an intermediate stage in the development of cholesteatoma, and Jordan (1963) reported on 11 cases in which cholesteatoma developed during the course of treatment for chronic secretory otitis media. The 165-patient series of MacKinnon (1971) contained 8 cholesteatomas. In the present material of 181 patients representing 323 ears the follow-up examination disclosed 4 cholesteatomas (1.4 %) of which 2 (0.7 %) can be considered a complication of tube therapy. During the tube therapy these 2 ears showed a purulent discharge which was not treated in any way. As a result of prolonged discharge both ears developed a marginal perforation and later a cholesteatoma. One patient, during the tympanostomy tube therapy developed an attic cholesteatoma in both ears as the result of retraction of Shrapnell's membrane.

A complication more frequent than cholesteatoma in the present material was persistent perforation. At the follow-up examination, 12 perforations were recorded, and additionally myringoplasty had been carried out in one ear for persistent perforation (total 4.5 %). The number of perforations considerably exceeded that reported by MacKinnon (1971) and by Mawson & Fagan (1972). The large number of perforations in the present series was apparently a result of the high rate of discharge. On the other hand, the purpose of tympanostomy therapy is to create a persistent perforation, and hence perforation should actually not be considered a complication. Closing the perforation operatively is not meaningful as long as there is a risk of the disease recurring.

In the material of Mawson & Fagan (1972) the most common drum change after tympanostomy tube therapy was tympanosclerosis (30 %). The next most common were retraction of the drum (21 %), atelectasis (9 %) and a visible tympanostomy scar (5 %). In their material only 18 % of the drums were normal at the follow-up examination. In the present material, 44.8 % of the drums treated with tympanostomy were normal or nearly normal in the follow up examination, 10.0 % were tympanosclerotic, 7.6 % pseudomembranous, 5.2 % scarred, 3.0 % atrophic, 2.1 % retracted, and 2.1 % adhered to the head of the stapes. The tympanostomy tubes were in position and ventilating in 22.1 %, a recurrence was seen in 3.1 %, purulent discharge from the tube in 1.7 % and complications in 7.6 %. The large proportion of normal drums in the present series compared with the above reports was probably rather a result of different criteria than better therapeutic results. In the group treated without tympanostomy 74.2 % of the drums were normal at the follow-up examination and 25.8 % were abnormal. 2 of the latter (6.5 %) were adhesive.

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At the follow up study the mean air conduction threshold of the total material was 12.3 dB and in 8 8 % of the ears the mean threshold of the speech frequencies exceeded 30 dB Accordingly the threshold of the speech frequencies for ears treated with tubes was at the follow up 11.3 dB or 1 8 dB higher than immediately after the insertion of the tubes The corresponding difference in the ears in which chronic secretory otitis media at the follow up was found to have healed was also 1 8 dB Although the difference is not statistically significant it probably gives a hint of drum changes produced by the tube therapy In the group of the ears treated without tympanostomy the mean air conduction threshold at speech frequencies was 22 8 dB on admission and 12.1 dB at the follow up The threshold had improved during treatment by 10 7 dB which is 5 1 dB less than in the group treated with tubes It is possible to obtain good results even without tubes, but the weekly paracentesis under general anaesthesia as suggested by Senturia (1958) is practically impossible in our circumstances, and furthermore unpleasant for the children. The risk always accompanying anaesthesia should not be underestimated. In addition to all of this the improvement of hearing achieved by paracentesis and aspiration may be of only a few days duration

The hearing results obtained are similar to those reported by Mawson & Fagan (1972) but definitely better than those reported by Kilby et al (1972) on a material of patients treated by a single unilateral paracentesis at the beginning of treatment and by insertion of a tympanostomy tube in the contralateral ear also only once at the beginning of treatment In both of Kilby's groups the air conduction threshold at speech frequencies was c 16 dB after the follow up period of 2 years.

The effectivity of the tympanostomy tube therapy which according to Palva et al (1974a, 1974b) is based on the drying effect of the air on the mucosa causing degeneration of glands and normalization of mucosa on one hand, and on the equalization of the negative pressure of the middle ear on the other appears to be indisputable in the treatment of chronic secretory otitis media. The permanent improvement of hearing achievable by means of the tympanostomy tubes is of decisive importance to children who are at the age when learning is most essential for their development.

6 CONCLUSIONS

Chronic secretory otitis media is the most common cause of hearing loss in children, and its increased incidence is partly a result of improved diagnosis while a part represents a true increase.

In most patients the onset of chronic secretory otitis media occurs before school age and in many at an age of less than one year

The cause of chronic secretory otitis media is, on the one hand, untreated or inadequately treated acute otitis media, and on the other a relative dysfunction of the Eustachian tube. Cleft palate patients form a risk group that requires regular otological observation from birth onwards.

In chronic secretory otitis media, the effusion is the final result of mucous gland activity released by infection. The effusion is mostly sterile. The sterility is attributable to a preceding antibiotic therapy or to the bactericidal and bacteriostatic effect of the effusion itself. Chronic secretory otitis media alone apparently does not lead to adhesive otitis but only if combined with recurrent suppurative infection.

The hearing loss in chronic secretory otitis media varies greatly but is in most cases so great that it adversely affects the child's development and his progress in school.

Hearing improvement following paracentesis is of short duration. After tympanostomy the hearing returns to the normal level and remains there unless the disease recurs after the extrusion of the tubes.

The removal of tympanostomy tubes is usually not advisable. The best thing is to let the tubes be spontaneously extruded and then observe whether the disease recurs. Most cases of chronic secretory otitis media heal with a tube therapy of less than a year's duration.

To keep track of complications and recurrences, the patients must be seen often enough during therapy and during at least one year after the tube therapy

Discharge is a common complication during tube therapy and it is apparently dependent on social conditions and the local climate.

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Possible complications arising in connection with tympanostomy tube therapy are marginal perforation and cholesteatoma. Also, chronic secretory otitis media may even in the course of tube therapy lead to the development of cholesteatoma of the attic.

7 SUMMARY

A material of 181 children (323 ears) with chronic secretory otitis media covering the 7 year period of 1965—71 is presented. 164 children (290 ears) were treated with tympanostomy tubes and 17 children (33 ears) conservatively with paracentesis. The patients attended a follow up examination in 1972 when special attention was devoted to the complications produced by chronic secretory otitis media and tympa nostomy tube therapy and to hearing losses

The onset of the symptoms of chronic secretory otitis media had usually occurred before school age The largest number of patients were under 1 year of age (18 9 %) at the onset, but almost the same number were 7—8 years olds (14 6 %) who had just started school

A total of 511 tympanostomy tubes were inserted, and 322 bacterial samples (198 ears) were taken in connection with the insertion 251 of them (78 %) were negative and 71 (22 %) positive. The most common bacteria were Hemophilus influenzae Staphylococcus aureus and Staphylococcus albus.

Purulent discharge was seen to accompany 124 tube treatments (25 %) Mastoidectomy had to be carried out on 15 ears (5 8 %) for prolonged suppurative discharge and the radiographic ear finding

At the follow-up examination which was carried out on average 3 years 2 months after the institution of tube therapy the chronic secretory otitis media was found to have healed in 190 ears (65 5 %) In 64 ears (22 1 %) the tubes were still in position and the patients were symptom free. In 9 ears (3 1 %) the disease had recurred in 5 ears (1 7 %) there was purulent discharge through the tubes and 22 ears (7 6 %) showed complications caused by chronic secretory otitis media and tube therapy The most common complication was persistent perforation, found in 13 ears (4.5 %) Cholesteatoma had developed during treatment in 4 ears (1 4 %) and 2 of these were attic cholesteatomas (0.7 %) (both in the same patient) The eardrum of the ears in which chronic secretory otitis media had healed was normal in 130 cases (68.4 %) and abnormal in 60 (31 6 %) The most common abnormal finding was tympanosclerosis.

In the conservatively treated group the eardrum status at the follow up examination was found to be normal in 23 ears (74 2 %) and abnormal in 8 ears (25 8 %) The worst drum changes were in a patient both of whose drums were adhesive and who had an air conduction threshold of 51 7 dB at speech frequencies in both ears

On admission for treatment the mean air conduction threshold (the mean value of 500 1000 and 2000 Hz) of the total material (161 ears) was 27 6 dB and at the follow-up examination (238 ears) 12.3 dB. The mean air conduction threshold improved during therapy by an average of 15.3 dB and the mean air bone gap diminished by 17.3 dB

In patients treated with tympanostomy tubes the mean air conduction threshold at speech frequencies was on admission (134 ears) 27 1 dB after insertion of the tubes (147 ears) 9.5 dB and at the follow up examination (202 ears) 11.3 dB During treatment the mean air conduction threshold improved by 15 8 dB and the mean air bone gap diminished by 16 4 dB

In the ears treated without tympanostomy the mean air conduction threshold at speech frequencies was on admission (18 ears) 22.8 dB and the follow-up (27 ears) 12.1 dB During treatment the mean air conduction threshold improved by 10 7 dB and the mean air bone gap diminished by 14 6 dB

In the total material, on admission the mean

air conduction threshold at speech frequencies was better than 15 dB in 21 1 % and poorer than 30 dB in 37 9 %. At the follow-up the threshold was better than 15 dB in 76.5 % of the ears and poorer than 30 dB in 8.8 %. The air conduction threshold at speech frequencies was found to be bilaterally poorer than 30 dB in 4 patients. Of these, 2 had a perceptive hearing loss exceeding 30 dB in both ears one had a manifest bilateral tympanal anomaly and the fourth a bilateral adhesive otitis as the result of neglected treatment.

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BY

TORSTI RANTANEN

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FROM THE OTOLARYNGOLOGICAL UNIVERSITY CLINIC
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I Introduction

The spread of infection from the nasal cavity into the paranasal sinuses is a common complication of colds. It has been estimated that 5 per cent of persons contract sinusitis (van Dishoeck, 1961). The sinus most often clinically affected is the maxillary sinus.

In addition to anatomical investigations, earlier research dealt with the bacteriology of sinusitis only recently have investigations of the function of the sinus and its ostium gained interest, this despite the fact that the first observation on the patency of the ostium was made as early as 1877 by Braune & Clasen. They observed that pressure changes produced by blowing air into the trachea of a cadaver were transmitted into the maxillary sinuses. Later Döderlein (1932) reported that these pressure changes inside the sinus depend on the intensity of respiration, while Proetz (1932) and Kerekes (1934) proved that respiratory pressure changes inside the sinuses and the nasal cavity correspond to each other when the ostium is open. However it was not until much later that patency tests based on this comparison were developed. In 1965 Drettner and in 1968 Cottle presented their patency tests. Like Proetz, Drettner performed the pressure recordings simultaneously using two manometers. Cottle used both simultaneous and consecutive recordings.

Another test of ostial function is measurement of ostial resistance. This method probably originates from the observation that different degrees of resistance can be felt even by hand at sinus irrigation. Flottes et al. (1960) performed their ostial resistance measurements by injecting air into the sinus and measuring the pressure that opened the ostium. Drettner (1965a) described a technique of measuring ostial resistance by using saline irrigation. He recorded the least amount of airpressure that made the irrigation fluid flow through the ostium into the nasal canal.

The patency test seems to have gained wider acceptance in clinical practice than resistance measurement, which was considered, for example by Zippel & Maier (1968) to have only relative value in practice.

I Introduction

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The patency test seems to have gained wider acceptance in clinical practice than resistance measurement, which was considered, for example by Zippel & Maier (1968) to have only relative value in practice.

II The aim of the study

This study was undertaken in order to investigate the relation of ostial function to clinical observations. A study in some detail of ostial function tests, the patency test and resistance measurement appeared necessary. Furthermore, possible changes in ostial function during the course of acute maxillary sinusitis were followed.

The results were treated in a way that would enable answers to the following questions to be attempted:

1. Can the investigated series be considered typical, as compared with earlier investigations on the etiology of the infection?
2. Is there any relation between the ache symptom and ostial patency and resistance to recovery?
3. Is there any relation between the x-ray findings and the results of the ostial function tests?
4. How should the criteria of a patent ostium be determined when the pressure changes are recorded consecutively?
5. Is a certain phase or procedure in connection with the maxillary sinus puncture preferable in determining ostial patency?
6. What is the importance of using sniffing and blowing in connection with a patency test?
7. Should ostial resistance be measured before or after irrigating the sinus?
8. What are the alterations of ostial patency in sinusitis?
9. What are the changes of resistance in sinusitis?

III Literature review

A. Ostial anatomy

There are variations in the diameter and length of the ostium. According to the investigations of Zuckerkandl (1893), Oppikofer (1906) and Schaeffer (1920) the diameter of the ostium varies from 1 to 22 mm. Aust & Drettner (1974a) ascertained that the mean functional diameter of the ostium in healthy persons is 2.4 mm. Simon (1939), who called the ostium canal, stated its length to be ≥ 3 mm in 83 % of cases, average length being 5.5 mm. According to Wagemann (1964) the length of the ostium is usually from 3 to 8 mm.

Accessory ostia between the maxillary sinus and the nasal cavity have been reported by Zuckerkandl in 10 %, by Oppikofer in 11 %, by Schaeffer in 44 %, by Myerson (1932) in 3 % and by van Alyea (1936) in 23 % of cases.

Zange (1940) stated that "Schwellgewebe" occurs not only in the turbinates, but also in the ostial area. He considered that this, on the one hand, protects the sinus against the spread of infection, but, on the other hand, causes drainage hindrances in maxillary sinusitis, as well as ex vacuo headache.

B. Bacteriology and roentgenology of maxillary sinusitis

According to many earlier bacteriological investigations, the frequency of respiratory pathogens in sinus secretion varies greatly. Some of these results are illustrated in Table 1. The most common respiratory pathogens are the Diplococcus pneumoniae and the Haemophilus influenzae. The frequency of sterile secretions varies from 17.2 to 24.7 %.

Ballantyne & Rowe (1949) stated, in connection with 206 unselected cases with chronic maxillary sinusitis, that there was no retention of secretion inside the sinus where no changes in the mucosa could be roentgenologically demonstrated. Where the mucosa was thickened, secretion was present in less than 10 % and in a homogeneously clouded sinus in 86 % of the cases. According to Hinde's (1950) largely similar result the frequency of the cases with secretion was 10 % where the mucosa was thickened. In a retrospective investigation of 27? cases with maxillary sinusitis by Vuorinen et al. (1962) secretion was disclosed in 86 % where the sinus was homogeneously clouded, and in 54 % where its mucosa was thickened. These

Table 1. Bacteriological findings in maxillary sinusitis in some earlier investigations (in %)

Investigator	Str. pyogenes	Dipl. pneumoniae	H. influenzae	Other bacteria	Sterile	No. of specimens
Urdal & Berdal 1949	6.2	30.5	30.9	1[illegible].4	24.7	81
Kortekangas 1963	4.6	45.1	20.6	3[illegible].9	1[illegible]7	306
Lystad et al. 1963	3.0	28.7	20.0	22.9	17.2	67
Hamory et al. 1971	2.1	10.9	3.7	61.6	16.6	192
Axelsson & Brorson 197[illegible]	2.0	21.9	1[illegible].7	41.8	21.6	202

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D Ostial resistance

I measuring ostial resistance, Flottes et al. (1960) used ai they did not, ho ever recommend pressures exceeding the ambient atmospheric pressures ith more than 200 mm H_2O because f the risk f air embolism. On the other hand, Soubeyrand (1964) pointed out that in subacute maxillary sinusitis the resistance is below that alue in only 6—1. % f ases. Consequently Drettner (1965a) and Zippel & Meyer (1968) used fluid instead f air in their resistance measurements. Their methods of measuring were similar.

Zippel & Meyer stated that in healthy persons normal resistance aries from 100 to 250 mm H_2O; in acute maxillary sinusitis resistance is normal in every other case, but elevated in the rest. Drettner pointed out that average resistance in sinusitis is 310 mm H_2O. Where there is retention of antral secretion, resistance is 420 mm H_2O on erage, whereas it is 150 mm H_2O in cases without secretion. He reported that t recovery from sinusitis ostial resistance becomes normal.

Rantanen & Kortekangas (1971) showed that at diagnostic puncture ostial resistance in sinusitis is more than 135 mm H_2O in every third case and less than that in the rest. Where the ostium as patent or partially patent for respiration, no elevation in resistance was noted in this in estigation in 60 % of the cases. On the other hand, when the ostium was obstructed during respiration, resistance was less than 135 mm H_2O in 43.5 % f the cases.

investigators found retention of secretion inside the sinus in 6 % of cases with a normal x ray finding. The corresponding results of McNeill (1963) were 83 %, 63 % and 20 % in an investigation of 150 cases with maxillary sinusitis.

Most of the above investigations illustrate the correlation between x ray findings and the presence of secretion inside the sinus in maxillary sinusitis. In order to demonstrate the retention of secretion inside the sinus in cases where the antral mucosa is thickened, more projections than the ordinary three or four are required in x raying. Axelsson et al. (19 0) in their investigation of 107 cases with maxillary sinusitis, reported secretion roentgenologically demonstrated inside the sinus in 24 % of cases with mucous membrane thickening, whereas this could be disclosed in 60 % through irrigation. When they added the fifth projection, the occipitomental with head horizontal and the affected side downwards, to the four standard projections, secretion was roentgenologically demonstrated in 88 % of the cases in which the puncture had been positive.

C. Ostial patency

Braune & Clasen (1877) reported changes of sinus pressure in their blowing experiment. Later Doderlein (1932) reported a decrease and increase of respiratory pressure inside the sinus in connection with empyema. Kerekes (1934) could not demonstrate these changes at the beginning of sinusitis, but they appeared at the recovery stage. After Proetz (1932) had observed that an open ostium transmits respiratory pressure changes from the nasal cavity into the sinus as unchanged, Flottes et al. (1960) stated that conclusions can be drawn about the ostial patency by comparing decrease and increase of respiratory pressures in the nasal cavity and the sinus.

Pressure measurements can be performed consecutively in the sinus and the nasal cavity or the nasopharynx. The disadvantage of these measurements is that the intensity of respiration continuously changes even in the same person. In order to eliminate this disadvantage simultaneous measurements have been used (Proetz, 1932; Drettner 1965b; Cottle 1968) in which decrease and increase of the respiratory pressure are measured simultaneously in the sinus and the nasal cavity or the nasopharynx. Drettner measured the pressures on both sides of the ostium by means of a trocar introduced into the sinus and a plastic catheter placed in the middle meatus on the same side. Cottle compared the pressure of the maxillary sinus with the pressure of the nasopharynx which he measured through a nozzle in the nostril opposite to the investigated side. Kortekangas (1970, 1974) proposed recording of the pressure difference between the maxillary sinus and the nasopharynx as part of the ostial patency test. In all the other methods, the deviation of pressure from the ambient atmospheric pressure is first measured, after which the pressure curves of the sinus and nasal cavity or the nasopharynx are mutually compared.

In acute sinusitis there are respiratory pressure changes inside the sinus in 23.2 %; in only 8.7 % however are the pressure changes identical in the nasal cavity and the sinus (Drettner 1965e). On the basis of these observations, Drettner divided the ostia into patent, partially obstructed and obstructed. He regarded the ostium as patent if during respiration, the decrease and increase of pressure in the plastic catheter and the trocar corresponded to each other. When the pressure changes inside the sinus were less pronounced than those in the nasal cavity the ostium was called partially obstructed. If there was no antral decrease or increase of the respiratory pressure, he regarded the ostium as obstructed. A partial obstruction can according to Drettner be caused by the ostium itself and also by the secretion that partially obstructs the ostium and/or the trocar. Rantanen & Kortekangas (1971) used the term partially patent for a partial obstruction, in a study comprising 36 maxillary sinusitis an ostial obstruction was reported in 65.0 % at diagnostic puncture, but at the end of treatment in only one case.

In addition to respiratory pressures, Drettner (1965b) also used pressures produced by sniffing and blowing, when evaluating the ostial patency. He reported an ostial obstruction for sniff/blow pressures in acute maxillary sinusitis in 47.8 % whereas sniffing and blowing opened an ostium obstructed for respiratory pressures in 25 % of the cases.

A valve phenomenon earlier observed by Proetz (193) Schmidtker (1932) and Kerekes (1934) was reported by Drettner (1965e) in an obstructed ostium in 13.2 % of the cases. Later the valve phenomenon was analysed by Drettner (1967).

D. Ostial resistance

In measuring ostial resistance, Flottes et al. (1960) used air; they did not, however recommend pressures exceeding the ambient atmospheric pressures with more than 200 mm H_2O because of the risk of air embolism. On the other hand, Soubeyrand (1964) pointed out that in subacute maxillary sinusitis the resistance is below that value in only 8—12 % of cases. Consequently Drettner (1965a) and Zippel & Meier (1968) used fluid instead of air in their resistance measurements. Their methods of measuring were similar.

Zippel & Meier stated that in healthy persons normal resistance varies from 100 to 250 mm H_2O. In acute maxillary sinusitis resistance is normal in every other case, but elevated in the rest. Drettner pointed out that average resistance in sinusitis is 310 mm H_2O. Where there is retention of antral secretion, resistance is 420 mm H_2O on average, whereas it is 150 mm H_2O in cases without secretion. He reported that at recovery from sinusitis ostial resistance becomes normal.

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Rantanen & Kortekangas (1971) showed that t diagnostic puncture ostial resistance in sinusitis is more than 135 mm H_2O in every third case and less than that in the rest. Where the ostium was patent or partially patent for respiration, no elevation in resistance was noted in this in estigation in 60 % f the cases. On the other hand, when the ostium was obstructed during respiration, resistance was less than 135 mm H O in 43.5 % f the cases.

investigators found retention of secretion inside the sinus in 0 % of cases with a *normal* x-ray finding. The corresponding results of McNeill (1963) were 83 %, 63 % and 20 % in an investigation of 150 cases with maxillary sinusitis.

Most of the above investigations illustrate the correlation between x-ray findings and the presence of secretion inside the sinus in maxillary sinusitis. *In order to demonstrate the retention of secretion inside the sinus in cases where the antral mucosa is thickened, more projections than the ordinary three or four are required in x-raying.* Axelsson et al. (1970) in their investigation of 19 cases with maxillary sinusitis, reported secretion roentgenologically demonstrated inside the sinus in 1 % of cases with mucous membrane thickening, whereas this could be disclosed in 60 % through irrigation. When they added the fifth *projection*, the occipitomental with head horizontal and the affected side downwards, to the four standard projections, secretion was roentgenologically demonstrated in 89 % of the cases in which the puncture had been positive.

C. Ostial patency

Braune & Clasen (1877) reported changes of sinus *pressure in their blowing experiment.* Later Döderlein (193) reported a decrease and increase of respiratory pressure inside the sinus *in* connection with empyema. Kerekes (1934) could not demonstrate these changes at the beginning of sinusitis, but they appeared at the recovery stage. After Proetz (1932) had observed that an open ostium transmits respiratory pressure changes from the nasal cavity into the sinus as unchanged, Flottes et al. (1960) stated that conclusions can be drawn about the ostial patency by comparing decrease and increase of respiratory pressures in the nasal cavity and the sinus.

Pressure measurements can be performed consecutively in the sinus and the nasal cavity or the nasopharynx. The disadvantage of these measurements is that the intensity of respiration continuously changes even in the same person. In order to eliminate this disadvantage simultaneous measurements have been used (Proetz, 193 ; Drettner 1965b; Cottle 1968) in which decrease and increase of the respiratory pressure are measured simultaneously in the sinus and the nasal cavity or the nasopharynx. Drettner measured the pressures on both sides of the ostium by means of a trocar introduced into the sinus and a plastic catheter placed in the *middle meatus on the same side.* Cottle compared the pressure of the maxillary sinus with the pressure of the nasopharynx, which he measured *through a nozzle in the nostril opposite to the investigated side.* Kortekangas (1970, 1971) proposed recording of the pressure difference between the maxillary sinus and the nasopharynx as part of the ostial patency test. In all the other methods, the deviation of pressure from the ambient atmospheric pressure is first measured, after which the pressure curves of the sinus and nasal cavity or the nasopharynx are mutually compared.

In acute sinusitis there are respiratory pressure changes inside the sinus in ... in only 8.7 %, however, are the pressure changes identical in the nasal cavity and the sinus (Drettner 1965c). On the basis of these observations, Drettner divided the ostia into patent, partially obstructed and obstructed. He regarded the ostium as patent if, during respiration, the decrease and increase of pressure in the plastic catheter and the trocar corresponded to each other. When the pressure changes inside the sinus were less pronounced than those in the nasal cavity, the ostium was called partially obstructed. If there was no antral decrease or increase of the respiratory pressure, he regarded the ostium as obstructed. A partial obstruction can, according to Drettner, be caused by the ostium itself and also by the secretion that partially obstructs the ostium and/or the trocar. Rantanen & Kortekangas (1971) used the term partially patent for a partial obstruction, in a study comprising 36 maxillary sinusitis, an ostial obstruction was reported in 55.6 % at diagnostic puncture, but at the end of treatment in only one case.

In addition to respiratory pressures, Drettner (1965b) also used pressures produced by sniffing and blowing when evaluating the ostial patency. He reported an ostial obstruction for sniff/blow pressures in acute maxillary sinusitis in 4.8 %, whereas sniffing and blowing opened an ostium obstructed for respiratory pressures in 3 % of the cases.

A valve phenomenon, earlier observed by Proetz (1932), Schmiedeker (1932) and Kerekes (1934), was reported by Drettner (1965c) in an obstructed ostium in 13. % of the cases. Later the valve phenomenon was analysed by Drettner (196).

V Methods

A. Clinical history and nasal state

Exact anamnestic information was obtained from all patients investigated. Attention was paid to earlier occurrence of maxillary sinusitis, as well as to the presence or absence of ache in the maxillary area, frequency and treatment of these and time elapsed from the last sinusitis. In addition to this, the relation between the present ache symptoms and ostial respiratory patency and resistance at diagnostic puncture, as well as duration of recovery were studied.

In nasal structure septal deformities and turbinal hypertrophies were observed. Cases with significant deformities were actually excluded from the investigation.

B. Bacteriology

In the sinusitis series bacteriologic samples, not controlled later on, were taken at diagnostic puncture. The sample was obtained through a trocar by sucking in 84 (71.2 %) cases and from irrigation dish, a so-called washed sample, in 34 (28.8 %) cases. The bacteria were studied by the usual bacteriological methods.

C. X-ray examination

X-ray examination of the sinuses was performed on the patients immediately before diagnostic puncture. It was not controlled later on. In the examination, anterior-posterior, lateral and occipitomental (Waters-Waldron) projections were used.

Thickness of the mucosa of the maxillary sinus was measured in the horizontal as well as in the vertical direction. In both measurements the thicknesses of the mucosa were summed, and the result compared with the respective diameter of the air space of the sinus.

The findings were defined as follows:

— *normal mucosa*, the mucosa could not be roentgenologically demonstrated or it was very thin
— *slightly thickened mucosa*: in both measurements the air space was wider in diameter than the summed thickness of the mucosa
— *markedly thickened mucosa*: in either one or both measurements the diameter of the air space was smaller than the summed thickness of the mucosa
— *fluid level*: at the bottom of the sinus there appeared an opaque horizontal clouding bordering the air space and remaining horizontal irrespective of the projection
— *homogenously clouded sinus*: no antral air space was demonstrated.

D. Ostial patency tests

1. Procedure

Before investigation the patient cleared his nose by blowing. After this nasopharyngeal and antral pressure changes during quiet nasal respiration were measured using the consecutive measuring technique, as well as antral pressure changes during sniffing and blowing, the so-called sniff/blow pressures. When nasopharyngeal and antral pressure changes were compared, only the peak values of the pressure decrease and increase were taken into consideration.

The investigation procedure was as follows (Fig. 1):

Step 1. The sinus was punctured under local anaesthesia (lidocaine 4 %) by introducing a Lichtwitz trocar (inner diameter 1.5 mm) through the inferior meatus.

Step 2. Respiratory pressure variations in the nasopharynx were recorded during quiet respiration using the anterior rhinomanometric technique (Fig. 1, I)

Step 3. The corresponding respiratory antral pressure variations were recorded through the Lichtwitz trocar by connecting it air-tightly to a manometer. The opposite nostril was closed with a finger (Fig. 1, II)

IV Material

The **sinusitis** series consisted of 86 patients with acute untreated maxillary sinusitis (Table 2). Investigation of ostial function and treatment of sinusitis were performed at the Department of Otolaryngology of the University Central Hospital of Turku during the years 1970—1971 simultaneously with the investigation of the control series. In 118 sinuses antral infection was apparent: in 54 patients this was unilateral, in 32 patients bilateral. There were 59 females (68.6 %) and 27 (31.4 %) males in the series. Their age varied from 12 to 77 years, mean age being 33.7 years, 32.7 years for females and 35.9 years for males.

Table 2. *Sinusitis series.*

	Unilateral testing	Bilateral testing	N of persons	N of sinuses
Female	34	25	59	84
Male	20	7	27	34
Total	54	32	86	118

The patients in the sinusitis series met the following requirements:
— they had symptoms of acute rhinitis
— the x-ray showed changes typical for acute maxillary sinusitis
— at diagnostic puncture retention of secretion was found.

The effect of drugs on sinusitis was not dealt with in this investigation. The treatment was, as can be seen from the methods, irrigation of the diseased sinus once a week. All patients were given the same nasal drops, xylometazolin chlorid. 0.1 % and 47 patients (60 sinuses) also received oral antibiotics, penicillin or tetracyclin, for a week.

Table 3. *Control series.*

	Unilateral testing	Bilateral testing	N of persons	N of sinuses
Female	13	8	21	29
Male	6	8	14	22
Total	19	16	35	51

The **control** series consisted of 35 patients at the same clinic, all of whom had agreed to the investigation of ostial function (Table 3). There were 21 (60 %) females and 14 (40 %) males. Altogether 51 sinuses were investigated. A unilateral investigation was performed for 19 patients and a bilateral investigation for 16. The age of the patients varied from 17 to 76 years, mean age being 37.5 years, 38.6 years for females and 35.3 years for males.

The patients in the control series met the following requirements:
— no active respiratory infection was observed
— no subjective nasal symptoms were reported
— at diagnostic puncture no retention of antral secretion was found.

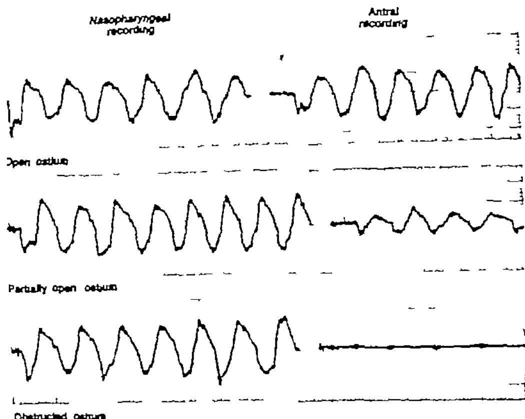


Fig. 2.
Comparison f nasopharyngeal and antral pressure variation in diff rent types f ostial patency Calibration mark equals 20 mm f water

ht t tl l evaluation.

A statistical comparison f the pressure ari- tion as made by observing the means f five successi peak alues f the inspiratory pres- sure decr se and the corresponding expiratory increase. Student t test as employed in this analysis. The nasopharyngeal and antral pres- ure ariation as considered to be equal hen $p > 0.01$

b. E aluation f sniff/blow test

I det rmining the o t i l p n t e, a term hich in the present study refers to the patency f the ostium in sniffing and blow ing, the peak lues f the pressure decrease and incre se d ring sniffing and blowing were ecorded. When the antral pressure change as mor than 60 mm H O the penetrance was regarded normal. If the pressure hange as 60 – 1 or 20—1 mm H O the penetrance as termed diminish d. I ddition to these, there ere cases in which the sniff/blow pressures did not produc any antral pressure change, i.e. there as no penetrance

Antral p r e s r t u r n to riginal le el after sniffing and blowing was estimated as follo (Fig. 3)

— *normal return* antral pressure occurring on sniffing or blowing returned to original level in ≤ 0.5 sec
— *delayed return* antral pressure returned to original level after sniffing or blowing, but the return took longer than 0.5 sec.
— *al e ph nom non* antral pressure did not return to original level after sniffing or blowing.

The s iff/bl w ffect on ostial re- spiratory patency as evaluated as follo s (Fig. 4)

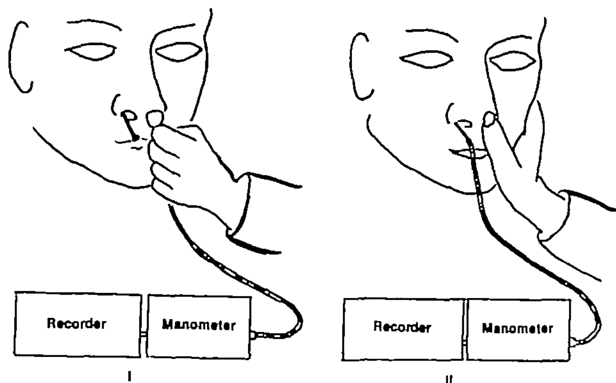


Fig 1

Arrangement of patency test.
I. Recording pressure variation in the nasopharynx (anterior rhinomanometry) Step 2
II Recording pressure variation inside the sinus (antral recording) Step 3

The recording of antral pressure was performed in the following three phases of each examination.

1 Native examination immediately after withdrawal of the stylet the trocar was connected air tightly to the manometer

2 Postauctional examination after taking the bacterial sample and cleansing the trocar by suction down to 0 4 Atm.

3 Postirrigation nal examination after irrigating the sinus (100 ml of 0.9 % physiological NaCl + 37°C) and leansing the trocar by the above-mentioned suction.

In all phases of measuring antral pressure decrease and increase were recorded, both during quiet respiration and sniffing and bl wing

An Elema Schonander EMT 33 electromanometer connected to a recording mingograph was employed. In the scale used, a pressure change of 2 mm H_2O corresponded to a deflection of 1 mm on the recording paper

— *Evaluation of findings*

a. Respiratory patency

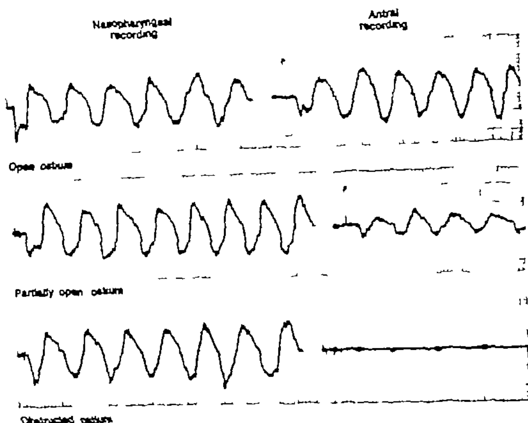
Clinical evaluation.

Means were calculated for five successive peak values of the inspiratory pressure decrease both in the nasopharynx and the sinus. The patency of the ostia was evaluated by comparing these means with each other (Fig)

— *open ostium* the mean of the antral inspiratory peak pressure decrease was at least 75 % of the corresponding peak pressure decrease of the nasopharynx

— *partially open ostium* a regular inspiratory pressure decrease occurred inside the sinus, but its mean was less than 75 % of the corresponding peak pressure decrease of the nasopharynx

— *obstructed ostium* no regular inspiratory pressure decrease occurred inside the sinus.



F g. 2.
C mparison f nasopharyngeal and antral pressure ariation in different types f ostial patency. Calibration mark equals 20 mm f water

S t t l evaluation.

A statistical comparison f the pressure variation as made by observing the means f five successi peak alues of the inspiratory pressure decre se and the corresponding expiratory increase Student t-test as employed in this analysis. The nasopharyngeal and antral pressure ariation as considered to be equal when p 0.01

b E aluation f sniff/blow test

I det rmining the t l p t s, term hich in the present study refers to the patency f the ostium in sniffing nd blowing, the peak alues f the pressure decrease and increase during sniffing and blowin, are recorded. Whe the tral pressure change was more than 60 mm H O the penetrance was regarded normal. If the pressure change as 60—1 20—1 mm H O the penetrance as termed *d minished*. In addition to these, there re cases in which the sniff/blow pressures did not produ ny antral pressure change i.e. there was *no pe trance*.

Antral p n retu n to original level fter sniffing and blo ing was estimated as follo (Fig. 3)

— *normal return* antral pressure occurring on sniffing or blowing returned to original level in ≦ 0.3 sec.
— *delayed return* antral pressure returned to riginal level afte sniffing or blowing, but the return took longer than 0.5 sec.
— *ral phenomenon* antral pressure did not ret rn to riginal level after sniffing or blowing.

The iff/bl w f f ct on ostial respiratory patency was evaluated as follo s (*Fig. 4*):

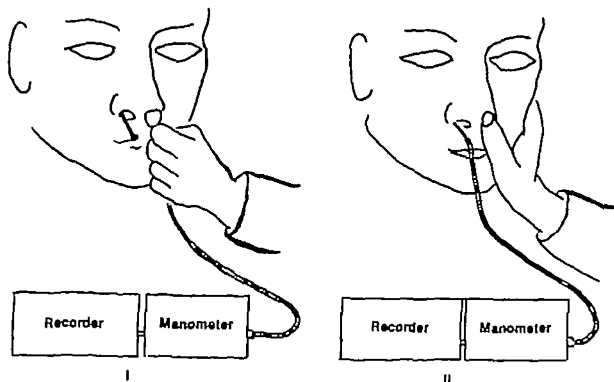


Fig. 1

Arrangement of patency test.
I. Recording pressure variation in the nasopharynx (anterior rhinomanometry) Step 2.
II. Recording pressure variation inside the sinus (antral recording) Step 3.

The recording of antral pressure was performed in the following three phases of each examination.

1. Native examination: immediately after withdrawal of the stylet the trocar was connected air tightly to the manometer.
2. Postsuctional examination: after taking the bacterial sample and cleansing the trocar by suction down to 0.4 Atm.
3. Postirrigational examination: after irrigating the sinus (100 ml of 0.9 % physiological NaCl, + 37°C) and cleansing the trocar by the above-mentioned suction.

In all phases of measuring antral pressure decrease and increase were recorded, both during quiet respiration and sniffing and blowing.

An Elema-Schonander EMT 31 electromanometer connected to a recording oscillograph was employed. In the scale used a pressure change of 2 mm H_2O corresponded to a deflection of 1 mm on the recording paper.

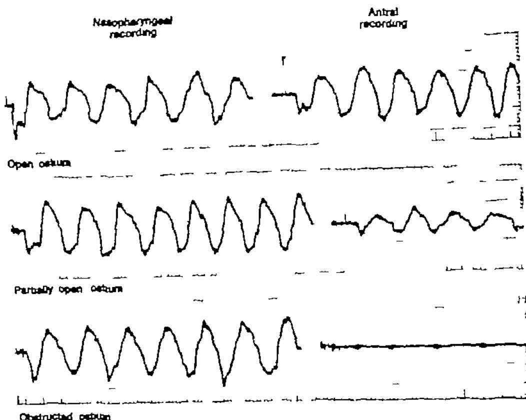
2. Evaluation of findings

a. Respiratory patency

Clinical evaluation.

Means were calculated for five successive peak values of the inspiratory pressure decrease both in the nasopharynx and the sinus. The patency of the ostia was evaluated by comparing these means with each other (Fig.)

— *open ostium*: the mean of the antral inspiratory peak pressure decrease was at least 75 % of the corresponding peak pressure decrease of the nasopharynx.
— *partially open ostium*: a regular inspiratory pressure decrease occurred inside the sinus, but its mean was less than 75 % of the corresponding peak pressure decrease of the nasopharynx.
— *obstructed ostium*: no regular inspiratory pressure decrease occurred inside the sinus.



F g. 2.

Comparison f nasopharyngeal and antral pressure variation in different types f ostial patency Calibration mark equals 20 mm of water.

St tist l evaluation.

A statistical comparison of the pressure vari- *ation was made by observing the means of five* successi peak alues of the inspiratory pressure decrease and the corresponding expiratory increase. Student t-test as employed in this analysis. The nasopharyngeal and antral pressure ariation was considered to be equal when $p > 0.01$.

b. E aluation f sniff/blow test

I determining the ti l p tran e, term hich in the present study refers to the patency f the ostium in sniffing and blowing, the peak values of the pressure decrease *and increase during sniffing and blo ing* were recorded. When the antral pressure change as more than 00 mm H_2O the penetrance was regarded normal. If the pressure change as 60—21 or 20—1 mm H_2O the penetrance as termed *d minished*. I addition to these, there were cases in which the sniff/blow pressures did not produ any antral pressure change, there was no *penetrance*

Antral p s t r to original level aft *sniffing* and *blo ing* was estimated as follow (Fig. 3)

- *normal return* antral pressure occurring on sniffing or blo ing returned to original level in $\leq$ 0.5 sec.
- *delayed ret rn* antral pressure returned to original level after sniffing or blowing, but the return took longer than 0.5 sec.
- *el ph nomenon* antral pressure did not return to riginal level after sniffing or blowing.

The iff/bl w ff t on ostial re*spiratory patency was evaluated as follo s* (Fig. 4):

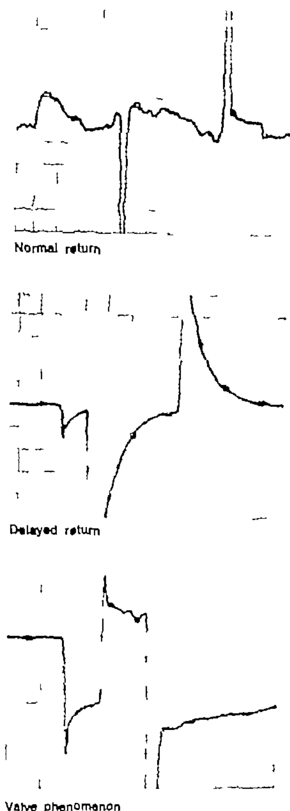


Fig 3
Antral pressure return to original level after sniffing and blowing. Calibration is the same as in Figure –

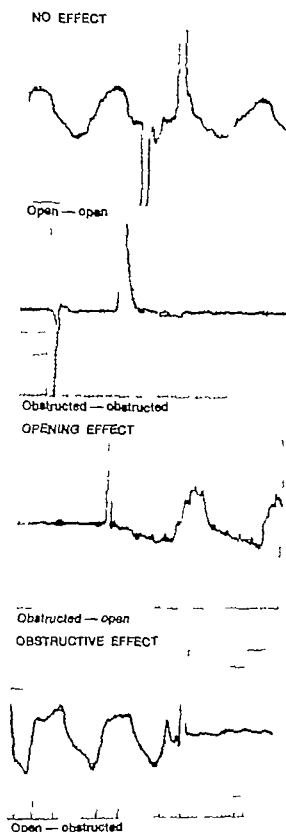


Fig 4
Effect of sniff/blow pressures on the ostial respiratory pattern. Calibration is the same as in Figure 2.

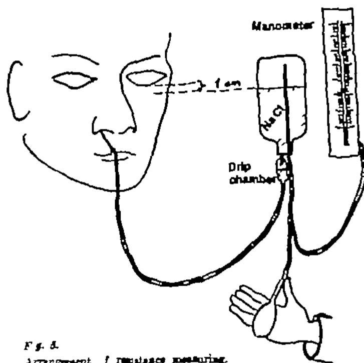


Fig. 5.
Arrangement f resistance measuring.

If antral respiratory variations remained equal to those *before sniffing or blowing*, the result was called *no-effect*. An *pos g ff ct* means that an obstructed ostium became open or partially open. Another possibility was that partially open ostium became open. An *obstructi ffect* means that an open ostium became only partially open or obstructed, also that partially open ostium became obstructed.

E. Ostial resistance measurements

1. *Procedure*

Measurements were performed before and after irrigation of the sinus. Before irrigation, measurement as taken f the smallest over pressure in the infusion bottle (saline, 0.9 %) needed to make the irrigation fluid and possible secretion flow through the ostium from the sinus into the nasal canal i.e. resistance before irrigation. The same measuring was repeated fter irrigation i.e. resistance fter irrigation.

At the beginning of resistance measurement, infusion bottle was fixed so that the fluid level as on the same level as the ostium, bout 1 cm beneath the inferior margin f the orbita. The bottle as connected with Licht-itz trocar by tubing (Fig. 5). The pressure inside the bottle was elevated with hand-pump if necessary. Pressure values were read from mercury manometer at the moment the fluid began to flow in the drip-chamber.

2. *E aluatio f results*

In evaluating resistance, the findings were grouped according to pressure values as follows 0—5 mm Hg, 6—50 mm Hg and higher than 50 mm Hg. When the pressure value was 0—5 mm Hg, the resistance was regarded normal. If the alue as 6—50 mm Hg, the resistance was regarded as *slightly elevated*, and value more than 50 mm Hg *markedly elevated*.

For patients in the si itis series, the ostial patency tests and resistance measurements were repeated weekly until recovery. Observations were made at diagnostic puncture and at the end of treatment, when the sinus was free f secretion and the infection cured. Observations not included in the above were considered to ha been made during treatment.

The patients in the contr l series were examined once.

In comparing results the Chi square test was used. In all cases the difference was called significant if $p < 0.05$.

VI Model experiments

A. Equipment and procedure

The aim of the model experiments was to obtain additional information about certain details of the ostial patency tests.

A model made of transparent plastic was used. It consisted of a nose component and a sinus component. The sinus component had three openings, two on the side of the nasal component, one on the lateral side. The posterior opening facing the nose component was filled with a rubber plug through which a Lichtwitz trocar (inner diameter 1.7 mm) was inserted in order to measure antral pressures. The anterior opening corresponding to the ostial canal was first closed air tightly with wax. The model ostia were made by perforating the wax with needles, the thickness of which varied from 0.05 to 4.5 mm. The length of the model ostia in the experiments referred to below was 1 mm, but even considerably longer model ostial canals gave very similar results. The only use of the lateral opening was cleaning of the ostial canal and the sinus component.

The tube of the respirator (Engström Modell 200) was air tightly connected to the posterior end of the nose component. The diameter of the circular anterior opening was 4.0 mm. The nose component and sinus component were air tightly connected.

The pressure measurements of the nose component were performed through the Lichtwitz trocar (Fig. 6 I). The peak values of the inspiratory/expiratory pressures were arranged to be 12/8, 24/16 and 48/32 mm H_2O in the nose component of the model. After the pressure changes in the nose component of the model had been stabilized the pressures inside the sinus component were measured through the Lichtwitz trocar (Fig. 6, II). By varying the size of the ostia the diameter of the smallest ostium was defined at which the peak values of the respiratory pressure change in the nose component corresponded to those inside the sinus component. The results were recorded and registered in the same way as in the actual study.

Sniffing and blowing were performed by the same person through the model, with or *of the nostrils closed (Fig. 6, III).* An attempt was made to always perform sniffing and blowing in the same way.

Two types of "secretion" were used in the model experiments: saline 0.9 % and mucus obtained by mixing and homogenizing nasal mucus from a number of healthy persons.

All measurements were repeated twice and results were identical. Where they were not identical a fault in the equipment was found.

B. Test results with model

Decrease and increase of the r e s p i r a t o r y p r e s s u r e s were transmitted from the nose component through the ostium into the sinus component as unchanged if the ostium was free of "secretion" and its diameter was ≧ 0.4 mm and when the inspiratory/expiratory pressure change in the nose component was 12/8 mm H_2O (Table 4). If this pressure change was 24/16 or 48/32 mm H_2O the diameter of the ostium had to be at least 0.5 mm for the pressure changes of the nose and sinus components to be identical. If the ostium was occluded by saline pressure changes in the nose and sinus components corresponded if the ostial diameter was 1.5 mm, when the respiratory

Table 4. *The smallest ostial diameter in mm for pressure changes in the nose and sinus components of the model to be equal*

Ostium	Inspiratory/expiratory peak pressure in mm H_2O		
	12/8	24/16	48/32
Ostium free of secretion	0.4	0.5	0.5
Saline in the ostium			
before suction	1.5	1.0	0.8
after suction	0.4	0.5	0.5
Mucus in the ostium			
before suction	—	—	—
after suction	0.4	0.6	0.6

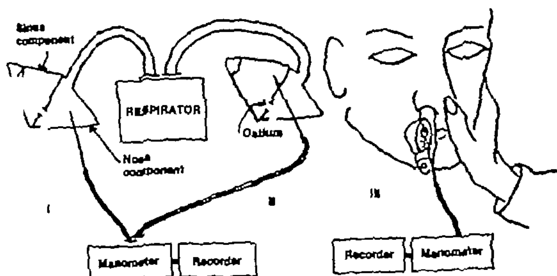


Fig 6
Arrangement of model recordings.

I. Recording of respiratory pressure in the nose component
II. Recording of respiratory pressures in the sinus component
III. Recording of sniff/blow pressures in the sinus component

pressure change was 12/8 mm H_2O. The diameters had to be 1.0 mm or 0.8 mm respectively when the pressure changes were 24/16 or 48/32 mm H_2O.

If the ostium was occluded by mucus, no regular respiratory pressure changes could be recorded inside the sinus component, even when the ostial diameter was 4.5 mm and respiratory pressure changes were 48/32 mm H_2O. When saline was sucked from the ostium through the Liebl.. trocar, the patency recordings after suction corresponded to those obtained with an ostium free of secretion. Patency recordings were also similar when mucus was sucked from the ostium and respiratory pressure changes were 12/8 mm H_2O. If pressure changes were 24/16 or 48/32 mm H_2O, the pressure changes of the nose and sinus components corresponded as long as the ostial diameter was at least 6.0 mm.

The pressure change inside the sinus component produced by sniffing and blowing was more than 60 mm H_2O if the ostial diameter was ≧ 0.2 mm, when the ostium was free of secretion or occluded with saline. If there was mucus in the ostium, the pressure change recorded inside the sinus component greatly depended on whether the mucus was mainly on the side of the sinus or on that of the nasal canal. If the mucus was mainly inside the sinus, a pressure decrease of more than 60 mm H_2O was produced inside the sinus on sniffing with the ostial diameter ≧ 3.5 mm on blowing, a corresponding pressure increase was produced, with the diameter ≧ 0.2 mm. If the mucus was mainly on the side of the nasal canal, a pressure decrease of more than 60 mm H_2O was produced inside the sinus on sniffing, with the ostial diameter ≧ 0.. mm and on blowing, a corresponding pressure increase was produced when the diameter was ≦ 1.0 mm.

When the ostium was free of secretion or occluded with saline, the pressure changes inside the sinus component after sniffing and blowing normally returned to the original level, if the ostial diameter was ≧ 0.5 mm. If the diameter was smaller the return was delayed. The return was also delayed when there was mucus in the ostium. In this case an air bubble, which slowly withdrew into the ostium, was produced on sniffing at the opening of the ostium on the

VI Model experiments

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All measurements were repeated twice and results were identical. Where they were not identical a fault in the equipment was found.

B. Test results with model

Decrease and increase of the respiratory pressures were transmitted from the nose component through the ostium into the sinus component as unchanged if the ostium was free of secretion" and its diameter was ≥ 0.4 mm and when the inspiratory/expiratory pressure change in the nose component was 12/8 mm H_2O (Table 4). If this pressure change was 24/16 or 48/32 mm H_2O the diameter of the ostium had to be at least 0.5 mm for the pressure changes of the nose and sinus components to be identical. If the ostium was occluded by saline pressure changes in the nose and sinus components corresponded if the ostial diameter was 1.5 mm when the respiratory

Table 4. *The smallest ostial diameter in mm, pressure changes in the nose and sinus components of the model being equal.*

Ostium	Inspiratory/expiratory peak pressure in mm H_2O		
	12/8	24/16	48/32
Ostium free of secretion	0.4	0.5	0.5
Saline in the ostium			
before suction	1.5	1.0	0.8
after suction	0.4	0.5	0.5
Mucus in the ostium			
before suction	—	—	—
after suction	0.4	0.6	0.6

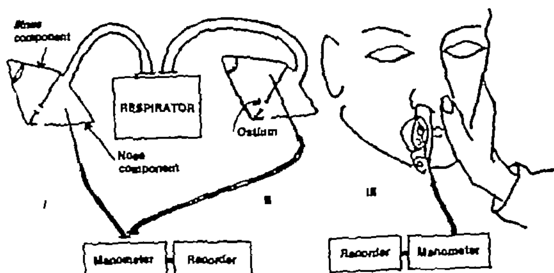


Fig. 6.
Arrangement f model recordings.

I. Recording of respiratory pressure in the nose component
II. Recording of respiratory pressures in the sinus component
III. Recording f sniff/blow pressures in the sinus component

pressure change was 1./8 mm H_2O The diameters had to be 1.0 mm or 0.8 mm respecti ely when the pressure changes were 14/16 or 48/32 mm H_2O

If the ostium was occluded by mucus, no regular respiratory pressure changes could be recorded inside the sinus component, even when the ostial diameter as 3.5 mm and respiratory pressure changes ere 48/32 mm H_2O When saline was sucked from the ostium through the Lichtwitz trocar the patency recordings after suction corresponded to those obtained with an ostium free f "secretion Patency recordings are also similar when mucus was sucked from the ostium and respiratory pressure changes ere 12/8 mm H_2O If pressure changes were 4/16 or 48/32 mm H_2O the pressure changes f the nose and sinus components corresponded as long as the ostial diameter as at least 0.6 mm.

The pressure change inside the sinus component produced by n ffing and blow g as more than 60 mm H_2O if the ostial diameter was $\geq$ 0.2 mm, when the ostium was free of secretion" occluded with saline. If there as mucus in the ostium, the pressure change recorded inside the sinus component greatly depended on whether the mucus was mainly on the side f the sinus or on that of the nasal canal. If the mucus was mainly inside the sinus, pressure decrease f more than 60 mm H_2O was produced inside the sinus on sniffing with the ostial diameter $\geq$ 3.6 mm on blo ing, corresponding pressure increase was produced, with the diameter $\geq$ 0.2 mm. If the mucus was mainly on the side of the nasal canal, pressure decrease of more than 60 mm H_2O was produced inside the sinus on sniffing, with the ostial diameter $\geq$ 0.2 mm and on blowing, a corresponding pressure increase w produced when the diameter was $\geq$ 3.0 mm.

When the ostium was free f secretion or occluded with saline, the pressure changes inside the sinus component after sniffing and blowing normally returned to the original level, if the ostial diameter was $\geq$ 0.5 mm. If the diameter as smaller, the return was *delayed. The return* was also delayed when there was mucus in the ostium. In this case an air bubble, which slowly ithdrew into the ostium, was *produced* on sniffing at the pening f the ostium on the

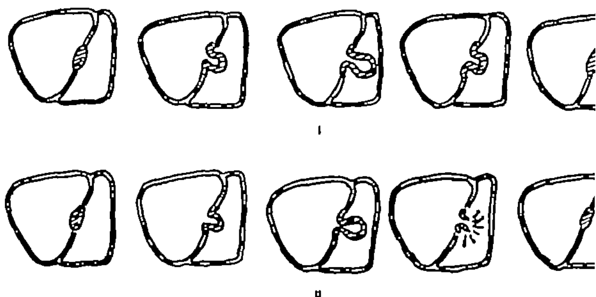


Fig 7
Changes in mucus at the ostium of the model during sniffing

I. Delayed return
II. Valve phenomenon

side of the nasal canal (Fig 7 I) On blowing a similar bubble appeared on the side of the sinus. The size of the bubble depended on the amount of mucus as well as on the intensity of sniffing and blowing. The ostial diameter appeared to have no effect on the frequency of delayed return.

The valve phenomenon did not occur if the ostium was free of "secretion" or occluded with saline. If there was mucus in the ostium, the phenomenon usually occurred, depending on the amount of mucus and the intensity of sniffing and blowing as well as on the size of the ostium. It was observed through the wall of the model that a valve appeared when the bubble produced on sniffing or blowing burst, and at once ostium again became occluded (Fig 7 II) this case, the pressure remaining inside sinus after sniffing was less than one at phere and after blowing greater than one mosphere. When sniff/blow pressures of o intensity were used, and when the amoun mucus in the ostium was the same, delayed turn and the valve phenomenon were freque observed, if the ostial diameter was ≤ 3.0 If the diameter was larger than this, the m did not occlude the ostium so frequently it remained open. If the valve was accompa by the delayed return of the sinus pres this was due to an air leak in the appara

VII Results

A. Clinical history and nasal state

I the sinu iti series 39.8 % ($^{47}/_{118}$) of the patients had earlier contracted maxillary sinusitis, in 20 cases three times or more. In 8.5 % (/$_{118}$) 1—3 months had elapsed from the last sinusitis, in the other cases more than three months. The infection had been treated in 40 cases ith series f puncture and drugs. In se en cases, only drugs had been given follo ing the diagnostic puncture.

Earlier ache had occurred once or more than once in 18.6 % ($^{22}/_{118}$) In 15 cases, the symptom had not been treated, and in seven cases drugs had been prescribed. One patient had vasomotor rhinitis. On this occasion, ache was localized in the sinus area in 60.2 % ($^{71}/_{118}$) Maxillary sinusitis was accompanied by acute frontal sinusitis in 3.4 % (/$_{118}$)

The size f the nasal cavity was normal in 77.1 % ($^{91}/_{118}$) Inferior turbinate hypertrophy as observed in 22.9 % ($^{27}/_{118}$) but only in 5.1 % (/$_{118}$) did it cause partial posterior obstruction of the nasal cavity

In the t l series, 23.5 % ($^{20}/_{85}$) of the patients had earlier contracted maxillary sinusitis. In all cases, over three months had passed since the last sinusitis. In seven cases, treatment had consisted f series f punctures and drugs in th cases, only drugs had been given follo ing the diagnostic puncture. Two patients f the control series reported that they had earlier experienced ache in the maxillary area. Possible maxillary sinusitis was not, how ever diagnosed. In the latter tw cases, no treatment had been gi en. N vasomotor rhinitis as f und in the patients investigated. N obstructiv septum deformities were detected. The turbinates were normal in 92.2 % ($^{47}/_{85}$) Inferior turbinate hypertrophy occurred in 7.8 % (/$_{85}$) but this did not obstruct the nasal canal.

B. Bacteriological findings

Bacteria ere isolated from the sinus secretion in 68.6 % ($^{81}/_{118}$) Respiratory pathogenic bacteria occurred in 58.4 % ($^{69}/_{118}$) (Table 5) Diplococcus pneumoniae was the most common bacterium, being found in 37.3 % ($^{44}/_{118}$) Haemophilus influenzae was found in 22.0 % ($^{26}/_{118}$) The secretion was sterile in 31.4 % ($^{37}/_{118}$)

T ble 5. *Bact riological findi gs.*

	No. of cases	Incidence in %
Respiratory pathogenic bacteria		
Str. pyogenes, Group A	1	
(ith Staph. aureus)	1	1.7
Dipl. pneumoniae	40	
(ith H. influenzae)	4	37.3
H. influenzae	19	
(with Staph. ureus)	1	
(with Str. viridans)	2	18.6
Klebsiella	1	0.8
Other pathogenic bacteria		
Staph. aureus	1	
(with Neiss. crassa)	1	
Str viridans	7	
Proteus mirabilis	1	8.5
Apathogenic bacteria		
Staph. epidermidis	2	1.7
Sterile	37	31.4
Total	118	100.0

C. X ray findings

There ere changes in all the sinuses f the i iti series (Table 6) The thickening of the mucosa was slight in 23.7 % ($^{28}/_{118}$) and marked in 21.. % ($^{25}/_{118}$) A fluid level as observed in 32.2 % ($^{38}/_{118}$) and the sinus was homogeneously clouded in 22.9 % ($^{27}/_{118}$)

A normal mucosa occurred in 64.7 % ($^{55}/_{85}$) in the t l series, and slight thickening of the mucosa in 33.3 % ($_{85}$) The sinus as homo neously cl uded in ..0 % ($_{85}$)

[illegible]

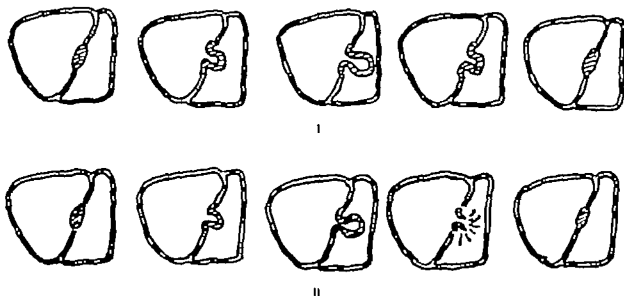


Fig 7
Changes in mucus at the ostium of the model during sniffing

I. Delayed return
II Valve phenomenon

side of the nasal canal (Fig 7 I) On blowing a similar bubble appeared on the side of the sinus. The size of the bubble depended on the amount of mucus as well as on the intensity of sniffing and blowing The ostial diameter appeared to have no effect on the frequency of delayed return.

The valve phenomenon did not occur if the ostium was free of secretion or occluded with saline. If there was mucus in the ostium, the phenomenon usually occurred, depending on the amount of mucus and the intensity of sniffing and blowing as well as on the size of the ostium. It was observed through the wall of the model that a valve appeared when the bubble produced on sniffing or blowing burst and at once the ostium again became occluded (Fig. 7 II) In this case, the pressure remaining inside the sinus after sniffing was less than one atmosphere and after blowing greater than one at mosphere. When sniff/blow pressures of equal intensity were used, and when the amount of mucus in the ostium was the same delayed return and the valve phenomenon were frequently observed, if the ostial diameter was ≤ 3.0 mm. If the diameter was larger than this, the mucus did not occlude the ostium so frequently and it remained open. If the valve was accompanied by the delayed return of the sinus pressure, this was due to an air leak in the apparatus.

Table 8. *All rations of ostial patency in the different phases of examinatio determined by statistical analyses f peak inspiratory and x pirat ry press e hanges in the nasopharynx and inside the sinus. Figures give the numbers of sinuses in hich the mean press e changes did or did not differ significantly by Student's t-test ($p < 0.01$)*

	During inspiration: Not significant	During inspiration: Significant	During expiration: Not significant	During expiration: Significant
Sinusitis series				
	All diagnostic punctures			
Native	19	99	17	101
Postunctional	29	93	20	92
Postirrigational	21	97	19	99
	During treatment			
Native	8	82	10	80
Postunctional	22	68	18	72
Postirrigational	16	76	17	73
	At end of treatment			
Native	57	61	51	67
Postunctional	58	59	65	53
Postirrigational	60	58	60	58
Control series (diagnostic puncture)				
Native	32	19	37	14
Postunctional	33	18	40	11
Postirrigational	34	17	30	21

both the inspiratory and expiratory pressures were transmitted in the same way through the ostium from the nose into the sinus.

In ele en cases, both the inspiratory and ex piratory v rage pressures are significantly higher inside the sinus than in the nasopharynx, the ostium being of course open in these cases (Table 9). In the statistical comparison of verage pressures of the nasopharynx and sinus, no significant difference was observed during inspiration in 11.9 % ($^{10}/_{84}$) and during ex piration in 22.6 % ($^{19}/_{84}$) when the ostium was partially open. In all other cases, the difference was significant.

In the c ntrol series, the ostium was pen natively in 58.8 % ($^{30}/_{51}$) postunctionally in 64. % ($^{33}/_{51}$) and postirrigationally in 70.6 % ($^{36}/_{51}$). With all the three phases f each examination included, the ostium was open in 80.3 % ($^{41}/_{51}$).

The statistical comparison of average pressure hanges f the sinus and nasopharynx revealed that the inspiratory pressure decrease in the nasopharynx was transmitted into the sinus as equal or as significantly decreased nati ely in 62.7 % ($^{32}/_{51}$) postunctionally in 64.7 % ($^{33}/_{51}$) and postirrigationally in 66.7 % ($^{34}/_{51}$) corresponding values for the expiratory pressure increase were 72.5 % ($^{37}/_{51}$) 78.4 % ($^{40}/_{51}$) and 58.8 % ($^{30}/_{51}$). No difference was recorded between inspiration and expiration in the mutual comparison f the results obtained at postunctional examination.

Table 9. *Clinically aluated ostial respiratory patency i relatio to statistical comparisons of the mea pressures in the nasopharynx and the sinus (t-test $p < 0.01$). Figures refer to numbers f sinuses and result det rmined postunctionally*

P t	Inspiration: Not significant	Inspiration: Significant, sinus	Inspiration: Significant, nasopharynx sinus	Expiration: Not significant	Expiration: Significant, sinus < nasopharynx	Expiration: Significant, sinus
Sinusitis series						
Open	93	3	11	79	19	11
Partially open	16	74		19	65	
Obstructed		133			135	
Control series (diagnostic puncture)						
Open	29	6	8	24	3	6
Partially open	5	12		14	7	
Obstructed		1			1	

Table 6. X ray findings of the sinuses

	No. of sinuses
Sinusitis series	
Mucosa normal	—
Mucosa slightly thickened	28
Mucosa markedly thickened	25
Fluid level	38
Sinus homogeneously clouded	27
Total	118
Control series	
Mucosa normal	33
Mucosa slightly thickened	17
Sinus homogeneously clouded	1
Total	51

D. Respiratory pressure variations in the nasopharynx

The nasopharyngeal pressure variation, recorded for reference purposes, was measured by anterior rhinomanometry after the trocar had already been inserted. For the sinusitis series, an average inspiratory pressure decrease of 14.80 mm H_2O and an expiratory pressure increase of 1_.60 mm H_2O were recorded. The corresponding figures for the control series were 14.2_ mm H_2O and 12.21 mm H_2O.

E. Results of ostial patency tests

1. *Respiratory patency*

a. Effect of suction and irrigation on ostial respiratory patency

In the sinusitis series, the ostium was open natively in 24.2 % (/) postsuctionally in 33.4 % (/) and postirrigationally in 20.1 % (/) (Table 7). Suction had no significant effect on ostial patency at diagnostic puncture or at the end of treatment. When the results obtained during treatment of sinusitis were mutually compared, it was noted that suction affected the ostial patency: the ostium was open at postsuctional examination significantly more often than at native examination (χ^2 = 7.73, df = 2). When the most normal one of the three observation results of each examination was chosen as the finding, the ostium was open in 43.3 % (/) partially open in 23.9 % (/) and obstructed in 32.8 % (/) of the sinusitis series. An open ostium occurred here significantly even more often than at the postsuctional examination, which usually gives the result closest to normal (χ^2 = _.71, df = 1).

Table 7. *Alterations in the ostial inspiratory patency at the different phases of the same examination. Figures give the numbers of sinuses examined*

	Ostial patency		
	Open	Partially open	Obstructed
Sinusitis series			
At diagnostic puncture			
Native	17	23	78
Postsuctional	26	25	67
Postirrigational	21	24	73
During treatment			
Native	7	19	64
Postsuctional	20	19	51
Postirrigational	16	4	50
At end of treatment			
Native	55	45	18
Postsuctional	63	40	15
Postirrigational	68	39	_1
Control series (diagnostic puncture)			
Native	30	20	1
Postsuctional	33	17	1
Postirrigational	36	11	4

When the average pressure changes of the nasopharynx and sinus were statistically compared, the inspiratory antral pressures were equal to, or had decreased significantly more than those of the nasopharynx natively in _5.8 % (/) postsuctionally in 35.6 % (/) and postirrigationally in 20.4 % (/) the corresponding values of the expiratory pressure increase were _3.9 % (/) 33.4 % (/) and 20.4 % (/) (Table 8). Also in the statistical comparisons of average pressure changes of the sinus and the nasopharynx the ostium was open for inspiratory pressures significantly more often at the postsuctional examination than at the native examination (χ^2 = 6.76, df = 1) during the treatment of sinusitis, but not at diagnostic puncture or at the end of treatment.

During expiration this difference was not observed. According to the postsuctional results

Table 8. *Alterations of ostial patency in the different phases of examination determined by statistical analysis of peak inspiratory and expiratory pressure changes in the nasopharynx and inside the sinus. Figures give the numbers of sinuses in which the mean pressure changes did or did not differ significantly by Student's t-test ($p < 0.01$).*

	During inspiration		During expiration	
	Not significant	Significant	Not significant	Significant
Sinusitis series				
At diagnostic puncture				
Native	19	99	17	101
Postpunctional	25	93	26	92
Postirrigational	21	97	19	99
During treatment				
Native	8	82	10	80
Postpunctional	22	68	18	72
Postirrigational	15	75	17	73
At end of treatment				
Native	57	61	51	67
Postpunctional	68	50	65	53
Postirrigational	60	58	60	58
Control series (diagnostic puncture)				
Native	22	12	37	14
Postpunctional	33	18	40	11
Postirrigational	34	[illegible]	30	21

both the inspiratory and expiratory pressures were transmitted in the same way through the ostium from the nose into the sinus.

In eleven cases, both the inspiratory and expiratory average pressures were significantly higher inside the sinus than in the nasopharynx, the ostium being of course open in these cases (Table 9). In the statistical comparison of average pressures of the nasopharynx and sinus, no significant difference was observed during inspiration in 11.9 % ([illegible]) and during expiration in 22.6 % ([illegible]) when the ostium was partially open. In all other cases, the difference was significant.

In the control series, the ostium was open natively in 58.8 % ([illegible]) postpunctionally in 64.7 % ([illegible]) and postirrigationally in 70.6 % ([illegible]). With all the three phases of each examination included, the ostium was open in 66.3 % ([illegible]).

The statistical comparison of average pressure changes of the sinus and nasopharynx revealed that the inspiratory pressure decrease in the nasopharynx was transmitted into the sinus as equal or as significantly decreased natively in 62.7 % ([illegible]) postpunctionally in 64.7 % ([illegible]) and postirrigationally in 66.7 % ([illegible]); corresponding values for the expiratory pressure increase were 72.5 % ([illegible]) 78.4 % ([illegible]) and 68.8 % ([illegible]). No difference was recorded between inspiration and expiration in the mutual comparison of the results obtained at postpunctional examination.

Table 9. *Clinically evaluated ostial respiratory patency in relation to statistical comparisons of the mean pressures in the nasopharynx and in the sinus (t-test $p < 0.01$). Figures refer to numbers of cases and results determined postpunctionally.*

Patency	During inspiration: Not significant	Significant: sinus	Significant: nasopharynx < sinus	During expiration: Not significant	Significant: sinus < nasopharynx	sinus
Sinusitis series						
Open	95	3	11	79	19	11
Partially open	10	4		19	65	
Obstructed		133			133	
Control series (diagnostic puncture)						
Open	20	6	8	4	3	6
Partially open	5	12		10	7	
Obstructed		1			1	

Table 6. X ray findings of the sinuses

	No. of sinuses
Sinusitis series	
Mucosa normal	—
Mucosa slightly thickened	28
Mucosa markedly thickened	[illegible]3
Fluid level	38
Sinus homogeneously clouded	27
Total	118
Control series	
Mucosa normal	33
Mucosa slightly thickened	17
Sinus homogeneously clouded	1
Total	51

D Respiratory pressure variations in the nasopharynx

The nasopharyngeal pressure variation, recorded for reference purposes, was measured by anterior rhinomanometry after the trocar had already been inserted. For the s i n u s i t i s series, an average inspiratory pressure decrease of 14.80 mm H_2O and an expiratory pressure increase of 1[illegible].50 mm H_2O were recorded. The corresponding figures for the c o n t r o l series were 14.2[illegible] mm H_2O and 12.21 mm H_2O

E. Results of ostial patency tests

1 *Respiratory patency*

a. Effect of suction and irrigation on ostial respiratory patency

In the s i n u s i t i s series, the ostium was open natively in 24.2 % ([illegible]) postsuctionally in 33.4 % ([illegible]) and postirrigationally in 29 1 % ([illegible]) (Table 7) Suction had no significant effect on ostial patency at diagnostic puncture or at the end of treatment. When the results obtained during treatment of sinusitis were mutually compared, it was noted that suction affected the ostial patency the ostium was open at postsuctional examination significantly more often than at native examination (x^2 = 7 73, df = [illegible]) When the most normal one of the three observation results of each examination was chosen as the finding, the ostium was open in 43.3 % ([illegible]) partially open

Table 7 *Alterations in the ostial inspiratory patency at the different phases of the same examination Figures give the numbers of sinuses examined*

	Ostial patency		
	Open	Partially open	Obstructed
Sinusitis series			
	At diagnostic puncture		
Native	17	[illegible]3	78
Postsuctional	26	25	67
Postirrigational	21	24	[illegible]3
	During treatment		
Native	7	19	64
Postsuctional	[illegible]0	19	51
Postirrigational	16	[illegible]4	50
	At end of treatment		
Native	55	45	18
Postsuctional	63	40	15
Postirrigational	58	39	[illegible]1
Control series (diagnostic puncture)			
Native	30	[illegible]0	1
Postsuctional	33	17	1
Postirrigational	38	11	4

in [illegible]3.0 % ([illegible]) and obstructed in 3[illegible].8 % ([illegible]) of the sinusitis series. An open ostium occurred here significantly even more often than at the postsuctional examination, which usually gives the result closest to normal (x^2 = 2.71 df = 1)

When the average pressure changes of the nasopharynx and sinus were statistically compared, the inspiratory antral pressures were equal to, or had decreased significantly more than those of the nasopharynx natively in [illegible]5.8 % ([illegible]) postsuctionally in 35.0 % ([illegible]) and postirrigationally in [illegible]9 4 % ([illegible]) the corresponding values of the expiratory pressure increase were [illegible]0 % ([illegible]) 33.4 % ([illegible]) and 20.4 % ([illegible]) (Table 8) Also in the statistical comparisons of average pressure changes of the sinus and the nasopharynx the ostium was open for inspiratory pressures significantly more often at the postsuctional examination than at the native examination (x^2 = [illegible], df = 1) during the treatment of sinusitis, but not at diagnostic puncture or at the end of treatment.

During expiration this difference was not observed. According to the postsuctional results

Table 8. *Alterations of ostial patency in the different phases of examination determined by statistical analysis of peak inspiratory and expiratory pressure changes in the nasopharynx and inside the sinus. Figures give the numbers of sinuses in which the mean pressure changes did or did not differ significantly by Student' t-test (p < 0.01)*

	Pressure difference between nasopharynx and sinus			
	During inspiration		During expiration	
	Not significant	Significant	Not significant	Significant
Sinusitis series				
	At diagnostic puncture			
Native	19	99	17	101
Postsuctional	26	92	26	92
Postirrigational	21	97	19	99
	During treatment			
Native	8	82	10	80
Postsuctional	22	68	18	72
Postirrigational	15	75	17	73
	At end of treatment			
Native	57	61	51	67
Postsuctional	68	60	65	53
Postirrigational	60	58	60	58
Control series (diagnostic puncture)				
Native	32	19	37	14
Postsuctional	33	18	40	11
Postirrigational	34	17	30	21

both the inspiratory and expiratory pressures were transmitted in the same way through the ostium from the nose into the sinus.

In eleven cases, both the inspiratory and expiratory average pressures were significantly higher inside the sinus than in the nasopharynx, the ostium being of course open in these cases (Table 9). In the statistical comparison of average pressures of the nasopharynx and sinus, no significant difference was observed during inspiration in 11.9 % ($^{14}/_{118}$) and during expiration in 22.0 % ($^{26}/_{118}$) when the ostium was partially open. In all other cases, the difference was significant.

In the control series, the ostium was open natively in 58.8 % ($^{30}/_{51}$) postsuctionally in 64.7 % ($^{33}/_{51}$) and postirrigationally in 70.6 % ($^{36}/_{51}$). With all the three phases of each examination included, the ostium was open in 56.3 % ($^{43}/_{51}$).

The statistical comparison of average pressure changes of the sinus and nasopharynx revealed that the inspiratory pressure decrease in the nasopharynx was transmitted into the sinus as equal or as significantly decreased natively in 62.7 % ($^{32}/_{51}$) postsuctionally in 64.7 % ($^{33}/_{51}$) and postirrigationally in 66.7 % ($^{34}/_{51}$) corresponding values for the expiratory pressure increase were 72.5 % ($^{37}/_{51}$) 78.4 % ($^{40}/_{51}$) and 58.8 % ($^{30}/_{51}$). No difference was recorded between inspiration and expiration in the mutual comparison of the results obtained at postsuctional examination.

Table 9. *Clinically evaluated ostial respiratory patency in relation to statistical comparisons of the mean pressures in the nasopharynx and in the sinus (t-test p < 0.01). Figures refer to numbers of sinuses and results determined postsuctionally.*

	Mean pressure differences between nasopharynx and sinus					
	During inspiration			During expiration		
Patency	Not significant	Significant sinus < nasopharynx, sinus		Not significant	Significant sinus < nasopharynx < sinus	
Sinusitis series						
Open	95	3	11	79	19	11
Partially open	10	74		19	65	
Obstructed		133			133	
Control series (diagnostic puncture)						
Open	20	5	8	4	3	6
Partially open	5	12		10	7	
Obstructed		1			1	

Table 6. X-ray findings of the sinuses

	No. of sinuses
Sinusitis series	
Mucosa normal	—
Mucosa slightly thickened	28
Mucosa markedly thickened	25
Fluid level	38
Sinus homogeneously clouded	27
Total	*118*
Control series	
Mucosa normal	33
Mucosa slightly thickened	17
Sinus homogeneously clouded	1
Total	*51*

D. Respiratory pressure variations in the nasopharynx

The nasopharyngeal pressure variation recorded *for reference purposes*, was measured by anterior rhinomanometry after the trocar had already been inserted. For the sinusitis series, *an average inspiratory pressure decrease of* 14.80 mm H_2O and an expiratory pressure increase of 12.50 mm H_2O were recorded. The *corresponding figures for the control series* were 14.22 mm H_2O and 12.21 mm H_2O.

E. Results of ostial patency tests

1. *Respiratory patency*

a. Effect of suction and irrigation on ostial respiratory patency

In the sinusitis series, the ostium was open natively in 24.2 % ([illegible]) postsuctionally in 33.4 % ([illegible]) and postirrigationally in 20.1 % ([illegible]) (Table 7). Suction had no significant effect on ostial patency at diagnostic puncture or at the end of treatment. When the results *obtained during treatment* of sinusitis were mutually compared it was noted that suction affected the ostial patency: the ostium was open at postsuctional examination significantly more often than at native examination (χ^2 = 7.73, df = 2). *When the most normal one of* the three observation results of each examination was chosen as the finding, *the ostium* was open in 43.3 % ([illegible]), partially open

Table 7. Alterations in the ostial inspiratory patency at the different phases of the same examination. Figures give the numbers of sinuses examined.

	Ostial patency		
	Open	Partially open	Obstructed
Sinusitis series			
	At diagnostic puncture		
Native	17	23	78
Postsuctional	26	25	67
Postirrigational	21	24	73
	During treatment		
Native	7	19	64
Postsuctional	20	19	51
Postirrigational	16	24	50
	At end of treatment		
Native	55	45	19
Postsuctional	63	40	15
Postirrigational	68	30	21
Control series (diagnostic puncture)			
Native	30	20	1
Postsuctional	33	17	1
Postirrigational	36	11	4

in 23.0 % ([illegible]) and obstructed in 32.8 % ([illegible]) of the sinusitis series. An open ostium occurred here significantly even more often than at the postsuctional examination, which usually gives the result closest to normal (χ^2 = 2.71, df = 1).

When the average pressure changes of *the nasopharynx and sinus were statistically compared*, the inspiratory antral pressures were equal to or had decreased significantly more than those of the nasopharynx natively in 23.8 % ([illegible]), postsuctionally in 35.6 % ([illegible]) and postirrigationally in 20.4 % ([illegible]); the corresponding values of the expiratory pressure increase were 23.9 % ([illegible]), 33.4 % ([illegible]) and 20.4 % ([illegible]) (Table 8). Also in the statistical comparisons of average pressure changes of the sinus and the nasopharynx the ostium was open for inspiratory pressures *significantly more often at the postsuctional* examination than at the native examination (χ^2 = 6.70, df = 1) during the treatment of sinusitis, but not at diagnostic puncture or at the end of treatment.

During expiration this difference was not observed. According to the postsuctional results

In sinusitis, no significant alterations took place in ostial respiratory patency until the sinus was free of secretion.

At diagnostic puncture, the ostium was found to be obstructed during respiration in 56.8 % and at the end of treatment in 12.7 % of cases.

2. *Sniff/blow test*

a. Ostial sniff/blow penetrance

In the sinusitis series, the ostial penetrance on sniffing at diagnostic puncture was normal natively in 23.0 % (³³/₁₄₃) both postsuctionally and postirrigationally in 30.4 % (⁴³/₁₄₁) (Table 11). The corresponding penetrance on blowing was normal natively in 18 % (²⁹/₁₅₉) postsuctionally in 33.6 % (⁴²/₁₂₅) and postirrigationally in 39.8 % (/₁₁₈) In all other cases, either the sniff/blow penetrance was diminished or there was no penetrance.

The sniff/blow penetrance during and at the end of treatment is presented in Table 11. The table shows that postirrigationally the sniff/blow penetrance was most frequently normal at diagnostic puncture and during treatment, but postsuctionally at the end of treatment. *Comparison of ostial penetrance recordings obtained at the native and postirrigational examination* indicate that suction and irrigation significantly improved the penetrance during treatment of sinusitis ($\chi^2 = 12.31$, df = 3)

In the control series the penetrance on sniffing was normal in all cases, both at the native and postsuctional examination. Post irrigationally the penetrance was diminished, 60—21 mm H O in 3.9 % (/₅₁) and normal in the rest. The penetrance on blowing was normal at the native and postsuctional examination in 96.1 % (⁴⁹/₅₁) In one case at the native examination there was no penetrance, in the rest the penetrance was diminished.

b. Return of sniff/blow pressures

In the sinusitis series, the return of antral pressure was normal after sniffing in 51.4 % (¹⁴³/₂₇₈) and after blowing in 40.8 %

T ble 11. *The penetrance of sniff/blow pressures into the maxillary sinus in the three phases of each examination. Pressure in mm H O Figures give the numbers of sinuses examined.*

	Sniff p.				Blow p.			
	60	60—1	30—1	0	> 60	60—31	30—1	0
Sinusitis series								
At diagnostic puncture								
Native	33	14	31	40	29	12	31	46
Postsuctional	43	0	26	40	42	10	21	45
Postirrigational	43	14	34	77	47		28	30
During treatment								
Native	30	13	16	31	20	9	18	37
Postsuctional	41	7	16	20	39	3	17	31
Postirrigational	43	13	16	18	45	4	21	20
At end of treatment								
Native	101	5	10	2	97	8	11	4
Postsuctional	102	5	4		10[illegible]	3	6	8
Postirrigational	100	7	6	5	93	6	8	8
Control series (diagnostic puncture)								
Native	51				40	1		1
Postsuctional	51				49	1	1	
	40	2			48	2	1	

b Alterations of patency

The ostium was obstructed in the s i n u s i t i s series significantly more often both at diagnostic puncture (χ^2 = 47.23, df = 2) and during treatment (χ^2 = 43.05, df = 2) than in the c o n t r o l series, when the ostial postsuctional patency was evaluated clinically (Table 7). At the end of treatment there was no difference between the ostial patency of these series. When the average inspiratory pressure decreases of the nasopharynx and the sinus were statistically evaluated a corresponding difference between the series was observed at diagnostic puncture (χ^2 = 26.60, df = 1) and during treatment (χ^2 = 20.52, *df* = 1) but not at the end of treatment, using results obtained at the postsuctional examination (Table 8). When expiratory pressure increases were compared between the series, the difference was significant at diagnostic puncture during and at the end of treatment (χ^2 = 45.25, 43.5 and 7.20, *df* = 1).

When alterations in the ostial patency were observed weekly, the patency was similar to that recorded at diagnostic puncture as long as there was antral retention of secretion (Table 10). If sinusitis was cured within the first two weeks, ostial patency was significantly better at the end of treatment than at diagnostic puncture (χ^2 = 46.20 and 17.13, df = 2). In cases in which the sinusitis was cured within the first week, the ostial patency was similar to that of the control series, but in cases cured within the second week, the difference between series was significant (χ^2 = 9.14, df = 2). If the treatment was continued, the ostial patency *differed significantly* from the patency of the control series during the first three weeks of treatment (χ^2 = 39.68, 29.99 and 20.0, df =).

At successive examinations, no change in the patency of the same ostium was observed in 48.0 % (/ₘₘ). An obstructed ostium became open or partially open, or a partially open ostium became open in 30.0 % (^{11}/ₘₘ). An open ostium became partially open or obstructed, or a partially open ostium became obstructed in 11.5 % (/ₘₘ). There were 37 cases in which a previously obstructed ostium was observed to be open at the following examination: this occurred after the first week of treatment in 16 cases and after the second week in 11 cases. In all these cases sinusitis had been cured. Of the 26 ostia open at diagnostic puncture three became obstructed during treatment. In two cases, the obstruction was present at all three phases of the examination; in the third case the ostium was open at the postirrigational examination.

Comment. Ostial respiratory patency should be examined after trials to eliminate the disturbing influence of secretion in the tubings between the tip of the trocar and the manometer or in the ostial canal itself by suction through the trocar.

Table 10. *Weekly alterations in ostial respiratory patency. Patency determined at postsuctional examination*

Patency	At diagnostic puncture	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks	After 5 weeks	No. of sinuses
Open	26						20
Partially open	25						23
Obstructed	67						67
		During treatment					
Open		13	3	4			20
Partially open		13	5	1			10
Obstructed		34	10	5			51
		At end of treatment					
Open		35	1	5	1	1	63
Partially open		20	12	3	4	1	40
Obstructed		9	0		3		15
No. of sinuses	118	118	60	18	10	[illegible]	3?0

In sinusitis, no significant alterations took place in ostial respiratory patency until the sinus was free of secretion.

At diagnostic puncture, the ostium was found to be obstructed during respiration in 56.8 % and at the end of treatment in 1..7 % of cases.

2. *Sniff/blow test*

a. Ostial sniff/blow penetrance

In the sinusitis series, the ostial penetrance on sniffing at diagnostic puncture was normal natively in 28.0 % ($^{33}/_{118}$) both postsectionally and postirrigationally in 36.4 % ($^{43}/_{118}$) (Table 11). The corresponding penetrance on blowing was normal natively in 24.0 % ($^{29}/_{118}$) postsectionally in 35.6 % ($^{42}/_{118}$) and postirrigationally in 39.8 % (/118) In all other cases, either the sniff/blow penetrance was diminished or there was no penetrance.

The sniff/blow penetrance during and at the end of treatment is presented in Table 11. The table shows that postirrigationally the sniff/blow penetrance was most frequently normal at diagnostic puncture and during treatment, but postsectionally at the end of treatment. Comparison of ostial penetrance recordings obtained at the native and postirrigational examination indicate that suction and irrigation significantly improved the penetrance during treatment of sinusitis ($\chi^2 = 12.31$, df = 3)

In the control series the penetrance on sniffing was normal in all cases, both at the native and postsectional examination. Post irrigationally the penetrance was diminished, 60—21 mm H_2O in 3.9 % (/51) and normal in the rest. The penetrance on blowing was normal at the native and postsectional examination in 96.1 % ($^{49}/_{51}$) In one case at the native examination there was no penetrance, in the rest the penetrance was diminished.

b. Return of sniff/blow pressures

In the sinusitis series, the return of antral pressure was normal after sniffing in 51.4 % ($^{182}/_{354}$) and after blowing in 49.8 %

Table 11. *The penetrance of sniff/blow pressures into the maxillary sinus in the three phases of each examination Pressure in mm H_2O Figures give the numbers of sinuses examined.*

	Sniff [illegible]				Blow [illegible]			
	> 60	60—21	20—1	[illegible]	> 60	60—21	20—1	0
Sinusitis series								
Native	33	14	31	40	29	12	31	46
Postsectional	43	9	26	40	42	10	21	45
Postirrigational	43	14	34	27	47	7	28	36
Native	30	13	16	31	28	9	18	37
Postsectional	41	7	16	28	39	3	17	31
Postirrigational	43	13	16	18	45	4	21	20
Native	101	5	10		97	6	11	4
Postsectional	102	5	4	7	102	3	5	8
Postirrigational	100	7	6	5	98	6	6	8
Control series (diagnostic puncture)								
Native	51				49	1		1
Postsectional	51				49	1	1	
Postirrigational	49	2			48	2	1	

Table 12. *Return of sniff/blow pressures. Figures refer to numbers of sinuses.*

	Return after sniffing				Return after blowing			
	Normal	Delayed	Valve	No antral pressure change	Normal	Delayed	Valve	No antral pressure change
Sinusitis series								
	At diagnostic puncture							
Native	36	30	12	40	39	18	15	46
Postsuctional	4[illegible]	21	15	40	3[illegible]	17	19	45
Postirrigational	38	[illegible]1	32	[illegible]7	35	18	29	30
	During treatment							
Native	26	17	16	31	23	[illegible]1	9	37
Postsuctional	40	12	1[illegible]	[illegible]8	38	13	8	31
Postirrigational	39	13	20	18	33	—	15	[illegible]0
	At end of treatment							
Native	98	7	11	2	97	10	7	4
Postsuctional	100	6	6	7	100	6	4	8
Postirrigational	84	7	22	5	85	0	16	8
Control series (diagnostic puncture)								
Native	49	1	1		50			1
Postsuctional	50	1			50	1		
Postirrigational	43	1	7		43	2	6	

([illegible]) (Table 12). It was delayed after sniffing in 13.6 % ([illegible]) and after blowing in 13.7 % ([illegible]). The ostium acted as a valve on sniffing in 14.9 % ([illegible]) and on blowing in 1[illegible].5 % ([illegible]). In comparing the different phases of the same examination, the valve was observed natively in 12.0 % ([illegible]) *on sniffing and in 9.5 % ([illegible]) on blowing.* Postsuctionally the valve was almost as common but postirrigationally the frequency was 2[illegible].7 % ([illegible]) on sniffing and 18.4 % ([illegible]) on blowing.

At diagnostic puncture the valve on sniffing was significantly more frequent after irrigation than at the native examination ($x^2 = 9.79$, df = 2). The situation was the same at the end of treatment both in sniffing ($x^2 = 10.85$, df = 2) and in blowing ($x^2 = 9.0[illegible]$, df = 2) comparing frequencies of postsuctional and postirrigational examinations. There was no difference between sniffing and blowing as regards the pressure return after irrigation.

In the control series, the return of pressure was normal at the native examination after sniffing in 96.1 % ([illegible]) and after blowing in 98.0 % ([illegible]). The return was normal after sniffing and blowing in 98.0 % ([illegible]) *at the* postsuctional examination and in 84.3 % ([illegible]) at the postirrigational examination. In all the phases of each examination the return was delayed in 2.0 % ([illegible]) after sniffing and in three cases after blowing. Two of these three occurred after irrigation and one after suction. The ostium acted as a valve natively in [illegible]0 % *([illegible]) and postirrigationally in 13.[illegible] % ([illegible])* on sniffing. After blowing the valve was seen only after irrigation in 11.8 % ([illegible]).

c. Effect of sniffing and blowing on ostial patency

In the sinusitis series, either an opening or obstructive effect on ostial patency occurred on sniffing in 8.6 % ([illegible]) and on blowing in 3.8 % ([illegible]) (Table 13). The difference between the effects of sniffing and blowing was significant when postirrigational results were mutually compared ($x^2 = 1[illegible].40$, df = 1).

The obstructive effect on sniffing occurred at the postsuctional examination significantly more often than at native examination ($x^2 = 11.06$, df = 1) or at the postirrigational examination ($x^2 = 6.58$, df = 1). Blowing did not have this effect.

Table 13. *The ffect f sniffing and blo ing on the ostial esp ratory patency. F gures refer t mbers of sinuses.*

	Eff t f sniff				Eff t f bl wi g			
	No effect	Opening effect	Obstructive effect	No antral pressure change	No effect	Opening effect	Obstructive effect	No antral pressure change
Sinusitis series								
Native	226	23	4	73	228	4		87
Postinctional	223	11	19	73	229	5	8	84
Postirrigational	235	20	7	64	249	8	5	64
Control series (diagnostic puncture)								
Nativ	51				50			1
Postinctional	51				51			
Postirrigational	50	1			50	1		

I the c t l series, both sniffing and blowing altered the ostial patency only once I both cases, an obstructed ostium became open.

Comment The ostial sniff/blow penetrance as most often normal afte the secretion had been removed from the sinus and the trocar by means of irrigation and suction. The post irrigational penetrance was normal at diag nostic puncture in 38.1 % and at the end of sinusitis treatment in 83.9 % the corresponding observ tion fo the control series was 95.1 % f cases.

The antral pressure return after sniffing and blo ing was normal most often postinctionally At diagnostic puncture, the return as normal in 33.5 % and at the end of treatment in 84.7 % In other cases of sinusitis, either delayed return or valve phenomenon oc curred, the latter being significantly more frequent postirrigationally In the control series, the return was normal in 98.0 % of cases.

Sniffing and blowing had an effect on ostial patency in 6.2 % of ases in the sinusitis and in 0 7 % in the control series.

F Ostial resistance

1. *Resistance bef re rrigation*

In the in sit s series, resistance as nor mal, 0—5 mm Hg, in 53.1 % ($^{173}/_{326}$) slightly levated, 6—50 mm Hg in 28.8 % ($^{94}/_{326}$) and markedly elevated, more than 50 mm Hg in 18.1 % ($/_{326}$) (Table 14) Resistance was nor mal before irrigation t diagnostic puncture in 28.0 % ($^{33}/_{118}$) during treatment in 47.8 % ($^{43}/_{90}$) and at the end f treatment in 82.2 % ($/_{118}$)

Table 14. *The distributio f sinuses in thre groups (0—5 6—50 > 50 mm Hg) f ostial resistance.*

	R						
	Before irrigation			After irrigation			
	0—5	6—50	> 50	0—5	6—50	> 50	No of sinuses
Sinusitis series							
At diagnostic puncture	33	52	33	58	58	2	/118
During treatment	43	29	18	62	28		/90
At end f treatment	97	13	8	11.	6		/118
No of sinuses	173	94	50	232	92		/326
Control series (diagnostic puncture)	51			51			/51

The weekly changes in resistance are presented in Table 15

In the control series, resistance was normal in all cases.

— Resistance after irrigation

In the sinusitis series, resistance after irrigation was normal in 71.2 % ($^{221}/_{311}$) slightly elevated in 28.2 % ($^{88}/_{311}$) and markedly elevated in 0 6 % ($^{2}/_{311}$) Resistance was normal at diagnostic puncture in 49 1 % ($^{58}/_{118}$) during treatment in 68.9 % ($^{62}/_{90}$) and at the end of treatment in 94.9 % (/118)

In the control series, ostial resistance after irrigation was normal in all cases.

Comment Normal ostial resistance corresponding to 0—5 mm Hg occurred before irrigation in 53.1 % and after irrigation in 71.2 %

Ostial resistance was normal in sinusitis at diagnostic puncture in 49.1 % and at the end of treatment in 94.9 of the cases.

Ostial resistance has to be measured after irrigation, since antral secretion obstructing the ostium results in errors in resistance measurements.

G. Recovery

Only cases of acute maxillary sinusitis that recovered were included in this investigation. The weekly cumulative recovery is presented in Table 21. After the first week of treatment no retention of secretion was revealed in 49.2 ($^{58}/_{118}$) After the second, the corresponding figure was 84.7 % ($^{100}/_{118}$)

Table 15 *Weekly changes of ostial resistance The resistance in mm Hg*

B al t n	At diagnostic puncture	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks	After 5 weeks	No. of sinuses
Before irrigation							
0 — 5	33						
6 — 50	52						
> 50	33						
After irrigation							
0 — 5	58						
6 — 50	58						
> 50	2						/118
	D l g t tm t						
Before irrigation							
0 — 5		32	7	4			
6 — 50		17	8	2	2		
> 50		11	3	4			
After irrigation							
0 — 5		43	11		1		
6 — 50		17	7	3	1		/90
	A d f t m t						
Before irrigation							
0 — 5		51	33	–	4	2	
6 — 50		–	4	1	1		
> 50			3		3		
After irrigation							
0 — 5		5	40	8	5	2	/118
6 — 50		1	2		3		

K. Comparisons between results of clinical observations, ostial patency tests and resistance measurements

1. Ache in relation to ostial patency, resistance and time of recovery

No inter-relation was observed between the ache symptom and ostial patency in acute maxillary sinusitis (Table 16).

Ostial resistance had no relation to the ache symptom in sinusitis (Table 17).

Time of recovery was independent of absence or presence of ache symptom in sinusitis (Table 18).

2. X-ray findings in relation to ostial patency and resistance

In the sinusitis series, the ostium was open in 39.3 % (/ₓ) partially open in 7.1 % (/ₓ) and obstructed in 53.6 % (/ₓ) when the antral mucosa was slightly thickened (Table 19). If the mucosa was markedly thickened, the corresponding figures were 12.0 % (/ₓ) 32.0 % (/ₓ) and 56.0 % (/ₓ). In cases where fluid level was roentgenologically demonstrated, the ostium was open in 29.3 % (/ₓ) partially open in 21.1 % (/ₓ) and obstructed in 52.6 % (/ₓ). If the sinus was homogeneously clouded, the ostium was open in 7.4 % (/ₓ) partially open in 25.9 % (/ₓ) and obstructed in 66.7 % (/ₓ).

Comparing the ostial patency in different x-ray findings, it was noted that the ostium was open significantly more often in cases where the antral mucosa was slightly thickened than in cases where either the antral mucosa was markedly thickened ($x^2 = 8.06$, $df = 2$) or the sinus homogeneously clouded ($x^2 = 9.27$, $df = 2$). There was no significant difference in patency if the antral mucosa was slightly thickened or there was a fluid level inside the sinus.

In the sinusitis series, resistance recordings before and after irrigation did not differ significantly from each other in different x-ray findings (Table 20).

In the control series, the ostium was open in 66.7 % (/ₓ) and partially open in 33.3 % (/ₓ) when the mucosa of the sinus was normal. If the mucosa was slightly thickened, the ostium was open in 58.8 % (/ₓ) partially open in 35.3 % (/ₓ) and obstructed in one case. The ostium of homogeneously clouded sinus was open.

Table 16. *Ache and ostial postural patency at diagnostic puncture*

	Ache present	Ache absent	No of sinuses
Patency			
Open	14	12	26
Partially open	16	9	25
Obstructed	41	26	67
No of sinuses	71	47	118
$x^2 = 0.82$, $df = 2$			

Table 17. *Ache and ostial resistance at diagnostic puncture.*

	Ache present	Ache absent	No of sinuses
Resistance in mm Hg			
Before irrigation			
0 — 5	1	16	33
6 — 50	31	21	52
> 50	22	10	33
After irrigation			
0 — 5	28	30	58
6 — 50	41	17	58
> 50			2
No of sinuses	/71	/4	/118
$x^2 = 1.81$, $df = 1$			

Table 18. *Ache and time of recovery*

	Ache present	Ache absent	No of sinuses
Time of recovery			
1 week	32	26	58
2 weeks	29	13	42
3 weeks	5	3	8
4 weeks		5	5
5 weeks	2		2
No of sinuses	71	47	118
$x^2 = 3.08$, $df = 3$			

The weekly changes in resistance are presented in Table 15.

In the control series, resistance was normal in all cases.

— *Resistance after irrigation*

In the sinusitis series, resistance after irrigation was normal in 71.2 % (²³²/₃₂₆) slightly elevated in 28.2 % (/₃₂₆) and markedly elevated in 0.6 % (/₃₂₆). Resistance was normal at diagnostic puncture in 49.1 % (⁵⁸/) during treatment in 68.9 % (⁶²/₉₀) and at the end of treatment in 94.9 % (/₁₁)

In the control series, ostial resistance after irrigation was normal in all cases.

Comment Normal ostial resistance corresponding to 0—5 mm Hg occurred before irrigation in 53.1 % and after irrigation in 71.2 %

Ostial resistance was normal in sinusitis at diagnostic puncture in 49.1 % and at the end of treatment in 94.9 of the cases.

Ostial resistance has to be measured after irrigation since antral secretion obstructing the ostium results in errors in resistance measurements.

G. Recovery

Only cases of acute maxillary sinusitis that recovered were included in this investigation. The weekly cumulative recovery is presented in Table 21. After the first week of treatment no retention of secretion was revealed in 49.2 % (⁵⁸/₁₁₈) After the second, the corresponding figure was 84.7 % (¹⁰⁰/₁₁₈)

Table 15 *Weekly changes of ostial resistance The resistance in mm Hg*

Resistance	At diagnostic puncture	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks	After 5 weeks	No of sinuses
Before irrigation							
0 — 5	33						
6 — 50	5						
> 50	33						
After irrigation							
0 — 5	58						
6 — 50	58						
> 50	2						/118
During treatment							
Before irrigation							
0 — 5		32	–	4			
6 — 50		17	8	2	[illegible]		
> 50		11	3	4			
After irrigation							
0 — 5		43	11	[illegible]	1		
6 — 50		17	7	3	1		/90
At end of treatment							
Before irrigation							
0 — 3		51	33	[illegible]	4	[illegible]	
6 — 50		7	4	1	1		
> 50			5		3		
After irrigation							
0 — 5		57	40	8	5	2	
6 — 50		1	2		3		/118

Table 21. *Recovery and ostial postinctional patency at diagnostic puncture.*

	P[atency]			Recovered sinuses in %		No. of sinuses
	Open	Partially open	Ob-structed	Weekly	Cumulative	
Time of recovery						
1 week	15	16	27	49..		58
2 [we]eks	8	6	28	70.0	84.7	42
3 [w]eeks	2	2	4	44.4	91.5	8
4 weeks	1	1	6	80.0	98.3	8
5 [w]eeks			2	100.0	100.0	
No. [o]f sinuses	26	25	67			118

If the ostium was obstructed, the penetrance [w]as normal in 19.4 % ($^{26}/_{134}$) on sniffing and in 16.0 % ($^{21}/_{131}$) on blowing. There was no penetrance on sniffing in 34.7 % ($^{46}/_{134}$) and on blowing in 44.4 % ($/_{131}$) In other cases the sniff/blow penetrance was diminished.

In comparing postirrigational results, in the [c]o[n]t[ro]l series the ostial penetrance on sniffing was normal [w]hen the ostium was open or partially open. In only tw[o] cases where the ostium was obstructed did diminished penetrance occur The penetrance was diminished on blowing once with open ostium and twice when the ostium [w]as obstructed during respiration. In the remaining cases the penetranc[e] was normal.

C[o]mment An open or partially open ostium al[wa]ys had sniff/blow penetrance, but in 10.7 % the penetrance [w]as diminished. An obstructed ostium had sniff/blow penetrance in 60.4 % but it was normal in only 1 7 % of the cases. Ostial respiratory obstructio[n] and no penetrance occurred simultaneously in 17.5 % in sinusitis.

5. *Ostial patency and antral pressure return [a]ft[er] sniffing and blowing*

In the s[i]nu[sit]i[s] series, return to original level was normal when the ostium was *open* in 92.6 % ($^{50}/_{54}$) after sniffing and in 89.5 % ($^{51}/_{57}$) after blowing (Table 23) When the ostium was partially open, the respective values were 67.8 % ($^{19}/_{28}$) and 60.9 % ($^{14}/_{23}$) With an obstructed ostium, return was normal in 14.9 % ($/_{94}$) after sniffing and in 18.8 % ($^{18}/_{96}$) after blowing, if only cases [w]ere taken into account where sniffing or blowing produced an antral pressure change.

Table 22. *Th[e] ostial sniff/blow penetrance [in] relation t[o] the ostial patency F[i]gures [a]r[e] for t[he] [nu]mbers [o]f sinuses at postirrigational examination.*

P	A[ntral pressure] 1[n] [mm H O] Sniffing > 80	80—?	20—?	0	[in] mm H O Blowing > 80	80—?	30—	0
Sinusitis series								
Open	92	3			93	2		
Partially [o]pen	68	13	8		4	7	6	
Obstructed	28	16	45	60	23	8	49	64
Control series (diagnostic puncture)								
Open	36				35	1		
Partially [o]pen	11				11			
Obstructed	2	2			2	1	1	

Table 19 X-ray findings and ostial postsuctional patency at diagnostic puncture

X-ray findings	Patency: Open	Partially open	Obstructed	No. of sinuses
Sinusitis series				
Mucosa slightly thickened	11	–	15	28
Mucosa markedly thickened	3	8	14	25
Fluid level	10	8	20	38
Sinus homogeneously clouded	2	7	18	27
No. of sinuses	26	23	67	118
Control series				
Mucosa normal	22	11		33
Mucosa slightly thickened	10	6	1	1[illegible]
Sinus homogeneously clouded	1			1
No. of sinuses	33	17	1	51

Comment The frequency of obstructed ostia was significantly higher in sinusitis if the x-ray examination revealed marked thickening of the antral mucosa or homogeneous clouding of the sinus, than if the antral mucosa was slightly thickened or there was a fluid level inside the sinus.

Conclusions cannot be drawn about ostial resistance by means of x-ray findings.

3 *Time of recovery and ostial patency*

When the ostium was open at diagnostic puncture 57.7 % (/[illegible]) of the sinusitis series were cured within a week (Table [illegible]1). When the ostium was partially open recovery occurred in 64.0 % (/[illegible]) and in 40.3 % (/[illegible]) if the ostium was obstructed. No significant difference between an open and an obstructed ostium was observed as regards the time of recovery. When the time of recovery and the ostial patency were observed during the following weeks, no difference as compared to the recovery of the first week, could be shown.

4 *Ostial patency and penetrance*

In the sinusitis series, the open ostium had diminished penetrance in two cases at diagnostic puncture and in one case during treatment (Table [illegible]2). In all other cases, sniff penetrance was normal. When the ostium was open blow penetrance was normal in all cases both at diagnostic puncture and during treatment. At the end of treatment blow penetrance was diminished in two cases.

If the ostium was partially open, the sniff/blow penetrance always produced an antral pressure change. The penetrance of sniffing was diminished in [illegible]1 % (/[illegible]) and in blowing in 14.9 % ([illegible]/[illegible]). In all other cases the sniff/blow penetrance was normal.

Table 20 X-ray findings and ostial resistance at diagnostic puncture

X-ray findings	Resistance in mm Hg: Before irrigation 0—5	6—50	> 50	After irrigation 0—5	6—50	> 50	No. of sinuses
Mucosa slightly thickened	9	11	8	13	14	1	/28
Mucosa markedly thickened	6	13	6	11	14		/25
Fluid level	12	14	12	[illegible]4	13	1	/38
Sinus homogeneously clouded	6	14	[illegible]	10	17		/27
No. of sinuses	33	52	33	58	58	2	/118

Table 25. *Ostial sniff/blow penetrance in relation to ostial resistance (mm Hg). Both determined after irrigation.*

Penetrance in mm H_2O	mm Hg 0—4	5—50	> 50	No. of sinuses
Sniff penetrance				
> 60	175	11		186
60 — 21	20	13	1	34
20 — 1	25	31		56
0	12	37	1	50
No. of sinuses	232	92	2	326
Blow penetrance				
> 60	176	14		190
60 — 21	11	6		17
20 — 1	26	29		55
0	19	43	2	64
No. of sinuses	232	92	2	326

If the ostial penetrance was normal, slightly elevated ostial resistance after irrigation was observed in 5.9 % (/186) on sniffing and in [illegible] % (/190) on blowing (Table 25). If there was no penetrance, resistance was normal in 24.0 % (/50) on sniffing and in 29.7 % (19/64) on blowing. In other cases resistance was elevated.

In the control series, resistance was normal in all cases before and after irrigation.

Comment. Ostial respiratory patency and resistance are intercorrelated. Resistance was normal in the open ostium in [illegible] % and in the obstructed ostium in 45.8 %.

When the ostial sniff/blow penetrance was normal, the resistance was also normal after irrigation in 93.4 %. If on the other hand, there was no penetrance, ostial resistance was normal in 27.2 % of the cases.

Table 23. Return of antral pressure after sniffing and blowing in relation to ostial patency determined postirrigationally. Figures refer to numbers of sinuses.

Patency	After sniffing: Normal	Delayed	Valve	% antral pressure change	After blowing: Normal	Delayed	Valve	% antral pressure change
Sinusitis series								
Open	88	1	0		85	3	–	
Partially open	60	10	18		53	15	19	
Obstructed	14	30	50	50	15	31	34	64
Control series (diagnostic puncture)								
Open	35		1		35		1	
Partially open	8		3		8	1	–	
Obstructed		2	3			1	3	

Return was delayed with an open ostium in 2.1 % ($^{4}/_{1xx}$) with a partially open ostium in 14.4 % ($^{?}/_{n}$) and with an obstructed ostium in 33.1 % ($^{4}/$) The valve frequencies were 0.8 % ($^{1}/_{1xx}$) 21.3 % (/ n) and 48.3 % ($^{44}/$ n) respectively

In the control series, pressure return to original level after sniffing and blowing was normal with open ostium in 97.[illegible] % ($^{44}/$) and with partially open ostium in 72.7 % (/) Of the four cases where the ostium was obstructed return was delayed in one case, and there was a valve in three cases both on sniffing and blowing.

Comment In sinusitis antral pressure return to original level after sniffing and blowing was most often not normal when the ostium was obstructed. The return was delayed in 21. % and the valve phenomenon occurred in 29 % of the cases with obstructed ostium.

6 Ostial patency and permeance in relation to ostial resistance

In the sinusitis series, resistance was normal before irrigation in the open ostium in 8[illegible] % ($^{?}/_{1xx}$) in the partially open ostium in 67.9 % ($^{57}/_{84}$) and in the obstructed ostium in 15.8 % ($^{?}/$) (Table 24) In the cases of elevated ostial resistance the incidence of marked elevation more than 50 mm Hg, was related to the degree of patency disturbance

After irrigation resistance was normal in the open ostium in 9 .9 % ($^{?}/$) in the partially open ostium in 83.9 % (/) and in the obstructed ostium in 45.8 % ($^{44}/$) In all other cases resistance was elevated. At the end of treatment resistance after irrigation was similar to that of the control series in the open ostium in all cases, in the partially open ostium in 9. 4 % ($^{44}/_{xx}$) and in the obstructed ostium in 70.[illegible] (/ n)

Table 24 Ostial patency at postirrigational examination in relation to ostial resistance (mm Hg)

Patency	Before irrigation: 0—5	6—50	> 50	No. of sinuses	After irrigation: 0—5	6—50	> 50	No. of sinuses
Open	95	13	1	109	93	2		95
Partially open	57	23	5	84	73	14		87
Obstructed	1	50	83	133	60	[illegible]	2	111
No. of sinuses	173	94	59	326	2[illegible]	[illegible]	2	320

Table 25. Ostial ff/blow penetrance i relation t ostial resistance (mm Hg) Both de t rmined after rrigation.

Penetrance in mm H_2O	R 0—5	6—50	> 50	No of sinuses
Sniff penetrance				
> 60	175	11		186
60 — 21	20	13	1	34
20 — 1	25	31		56
0	12	37	1	50
No. of sinuses	232	92	2	326
Blow penetrance				
> 60	176	14		190
60 — 21	11	6		17
20 — 1	28	20		56
0	19	43	2	64
No. f sinuses	232	92	2	326

If the ostial penetrance was normal, slightly elevated ostial resistance after irrigation was observed in 5.9 % ([11]/[186]) on sniffing and in 4 % (/[190]) on blowing (Table 25) If there was no penetrance, resistance was normal in 24.0 % (/[50]) on sniffing and in 29.7 % ([19]/[64]) on blowing. In other cases resistance was elevated.

In the o n t r o l series, resistance was normal in all cases before and after irrigation.

C mment Ostial respiratory patency and resistance are intercorrelated. Resistance was normal in the open ostium in 97.9 % and in the obstructed ostium in [illegible].8 %

When the ostial sniff/blow penetrance was normal, the resistance was also normal after irrigation in 93.4 % If, on the other hand, there was no penetrance, ostial resistance was normal in [illegible].2 % of the cases.

Table 23. Return of antral pressure after sniffing and blowing in relation to ostial patency determined postirrigationally. Figures refer to numbers of sinuses.

Patency	After sniffing: Normal	Delayed	Valve	No antral pressure change	After blowing: Normal	Delayed	Valve	No antral pressure change
Sinusitis series								
Open	88	1	6		85	3	[illegible]	
Partially open	59	10	18		53	16	19	
Obstructed	14	30	50	50	15	31	34	64
Control series (diagnostic puncture)								
Open	35		1		35		1	
Partially open	8		3		8	1	[illegible]	
Obstructed		1	3			1	3	

Return was delayed with an open ostium in 2.1 % (/[illegible]) with a partially open ostium in 14.4 % ([illegible]/[illegible]) and with an obstructed ostium in 35.1 % ([illegible]/). The valve frequencies were 0.8 % ([illegible]/[illegible]), 21.3 % (/[illegible]) and 48.3 % ([illegible]/[illegible]) respectively.

In the **control** series, pressure return to *original level after sniffing and blowing* was normal with open ostium in 97.2 % ([illegible]/[illegible]) and *with partially* open ostium in 72.7 % (/[illegible]). *Of the four cases where the ostium was obstructed*, return was delayed in one case, and there was a valve in three cases both on sniffing and blowing.

Comment. In sinusitis antral pressure return to original level after sniffing and blowing was most often not normal when the ostium was obstructed. The return was delayed in 21.2 % and the valve phenomenon occurred in 20.2 % of the cases with obstructed ostium.

6. *Ostial patency and resistance in relation to ostial resistance*

In the **sinusitis** series, resistance was normal before irrigation in the open ostium in *87.2 %* ([illegible]/[illegible]) *in the partially open ostium* in 67.9 % (/[illegible]) and in the obstructed ostium in 16.8 % ([illegible]/[illegible]) (Table 24). In the cases of elevated ostial resistance the incidence of marked elevation, more than 50 mm Hg, was related to the degree of patency disturbance.

After irrigation resistance was normal in the open ostium in 97.9 % ([illegible]/[illegible]), in the partially open ostium in 83.9 % ([illegible]/[illegible]) and in the obstructed ostium in 46.8 % ([illegible]/[illegible]). In all other cases resistance was elevated. At the end of treatment resistance after irrigation was similar to that of the control series in the open ostium in all cases, in the partially open ostium in 97.4 % ([illegible]/[illegible]) and in the obstructed ostium in [illegible] % (/[illegible])

Table 24. *Ostial patency at postirrigational examination in relation to ostial resistance (mm Hg)*

Patency	Before irrigation: 0–5	6–50	> 50	No. of sinuses	After irrigation: 0–5	6–50	> 50	No. of sinuses
Open	95	13	1	109	93	[illegible]		95
Partially open	57	22	5	84	73	14		87
Obstructed	21	59	63	143	66	6	[illegible]	111
No. of sinuses	173	94	69	336	232	[illegible]	2	3[illegible]3

A disadvantage of consecutive measuring is that the peaks of both pressure decrease and increase developed during respiration continuously fluctuate, even in the same person. In present study 25 % was chosen as the limit within which this fluctuation was allowed to vary, i.e. the ostium was still considered open when the mean peaks of antral pressure decrease during inspiration were at least 75 % of the corresponding inspiratory pressure decrease in the nasopharynx. The pressures of the nasopharynx and the sinus were compared with each other using the means of five inspiratory pressure decreases.

This rough estimate of the means was proved appropriate by a study in which individual variation was also statistically analysed and compared at the significance level of 0.01.

Model experiments were arranged to study some details pertaining to the patency test. It was shown that a circular ostrum with as narrow a diameter as 0.5 mm transmitted respiratory peak pressures unchanged from the nasal cavity into the sinus. In the patency tests with the model, secretion had a decisive influence on the results of measurement of the sinus pressures. It was observed that ostial obstruction caused by secretion disappeared when the secretion was removed by sucking through the trocar.

In the sinusitis and control series of the present study ostial patency was tested in three phases of the same examination, namely postsuctionally and postirrigationally. The latter measurement was performed after careful removal by suction of the irrigation fluid and possible secretion. Observations made in the same phase of examination were best suited for comparison, and results most representative of ostial patency was tested postsuctionally and ostial penetrance for sniffing and blowing postirrigationally. The difference between results of patency and penetrance testing was due to the different pressures used in testing ostial patency and penetrance.

Ostial respiratory obstruction is due either to the swelling of mucosa and/or to secretion in the tubing or ostial canal. The respiratory patency test takes both possibilities into consideration simultaneously. The use of sniff/blow pressures has a decisive influence in revealing causes of the obstruction. A swollen mucous membrane can be considered a cause of ostial obstruction, if sniff/blow pressures cannot be recorded inside the sinus. It is further possible that ostial obstruction is caused by secretion, even though no antral sniff/blow pressures can be recorded.

Ostial obstruction caused by mucous membrane swelling and secretion occurred in present study in 40.8 % and obstruction caused by mucous membrane swelling only in 1.5 %.

Disturbances of patency such as valve phenomenon and delayed return of pressure in the penetrance test after sniffing and blowing, are interpreted only as signs of secretion.

When the ostial resistance was measured before the sinus secretion had been irrigated away the united resistance of the ostium and the secretion was recorded. A most representative result for the ostial resistance only was obtained when resistance was measured after irrigation. In present sinusitis series, resistance was normal, 0—5 mm Hg, before irrigation in 53.1 % and after irrigation in 71.2 %.

2. *Ostial patency in sinusitis*

According to Drettner (1965a) an ostial obstruction for respiration is present in acute maxillary sinusitis in 76.8 % and for sniffing and blowing here indicated by the term penetrance, in every other case. In this series, the corresponding figures were 32.8 % and 1.5 % taking the best patency of the three phases of the examination and the penetrance after the irrigation into account.

A valve phenomenon or delayed return in the penetrance test occurred in 60.4 % of these cases of the present sinusitis series in which the ostium was obstructed for quiet respiration. The valve occurred in this series twice as often as in that of Drettner (1965a).

The discrepancies between results of the series of Drettner and of present study are apparently due to different methods of investigation, different evaluation of results and also differences in the series. In the present study ostial patency was examined only in reversible cases of acute maxillary sinusitis. Further the details of the examination, the exact phase and relation to irrigation and trials to eliminate the effect of secretion were not given in Drettner' series. The most important reason for the differences between Drettner' and the present results is presumably secretion, to which special attention has been paid in this study.

VIII Discussion

A Bacterial findings of sinus secretion

The bacteriological findings in the present series of 118 cases of acute maxillary sinusitis may be considered to correspond to the earlier studies (Urdal & Berdal 1949 Kortekangas, 1963 Lystad et al., 1963 Meinecke 1971 and Axelsson & Brorson 1972) when account is taken of the fairly large variation in the frequencies of different bacteria.

B. Ache in relation to ostial patency resistance and recovery

Flottes et al. (1960) and Drettner (1960) observed that test subjects had no ache even though the antral pressure was decreased to 300—400 mm H_2O below the ambient atmospheric pressure. This, of course, is only possible when the ostium is obstructed.

Sluder's (1927) conclusion that ache results from an antral pressure decrease caused by oxygen resorption was recently partly confirmed by Aust & Drettner (1974b) who found some correlation between pain in the region of the paranasal sinuses and low oxygen content inside the sinus.

This series agrees with Drettner's (1966) observation that ache symptom and ostial patency are not mutually correlated. Further in this series no conclusions can be drawn about the ostial resistance and the time of recovery on the grounds of the ache.

C. X ray findings in relation to ostial patency and resistance

The more marked the x ray changes, the more probable is the presence of secretion in the sinus (Hinde, 1950 Vuorinen et al., 1962 McNeill 1963). When a fifth projection, occipitomental with the head horizontal and the affected side downwards, is added to the so-called standard projections, occipitofrontal occipitomental full axial and lateral, antral secretion can be demonstrated by means of x ray examination in 88 % of cases in which antral mucous membrane thickening is seen and the puncture positive (Axelsson et al., 1970).

In this series, using three standard projections, the presence of secretion was demonstrated by x ray in only every third case, although changes were seen in all of them.

Thus, to my knowledge is the first study in which x ray findings have been compared with the results of ostial patency and resistance tests. According to present observations, an ostial obstruction was significantly more frequent in cases in which marked mucous membrane changes were present or the sinus was homogeneously clouded than in cases in which the mucous membrane changes were slight or in which there was an antral fluid level. From this observation, it can be concluded that the antral mucous membrane changes, i.e. swelling extend into the ostium producing similar alterations in the ostial patency.

As discussed in the next chapter respiratory obstruction in the ostium can be due to secretion, as well as to thickening of the mucous membrane of the ostium. The observation that ostial resistance was independent of x ray findings supported the opinion that respiratory obstruction in the ostium is often caused by secretion in the ostium.

D Ostial patency

1 *Methods*

Ostial patency test is a comparison of pressure variation inside the sinus and the corresponding nasal cavity or nasopharynx. These pressures can be recorded either consecutively or simultaneously. With simultaneous recording, introduction of a catheter in the middle meatus as in Drettner's (1965c) technique can be difficult and often cause discomfort to the patient. For this reason, a consecutive recording was chosen in the method of this study and the reference pressure was recorded by means of the anterior rhinomanometric technique.

A disadvantage f consecutive measuring is that the peaks of both pressure decrease nd increase developed during respiration continuously fluctuate, even in the same person. In present study 25 % was chosen the limit within which this fluctuation was allowed t ary i.e. the ostium still considered pen hen the mean peaks of tral pressure decrease during inspiration ere at least 75 % of the orresponding inspiratory pressure decrease in the nasopharynx. The pressures of the nasopharynx and the sinus ere compared with each other using the means f the inspiratory pressure decreases.

This rough estimat of the means as proved ppropriate by study in hich individual ariation as lso statistically analysed and compared t the significance le el of 0.01.

Model experiments ere arranged to study some details pertaining to the patency test. It as show that ircular ostium with as narrow diameter as 0.5 mm transmitted respiratory peak p essures unchanged from the nasal cavity into the sinus. In the patency tests ith the model, secretion had decisi influence n the results t measurement of the sinus pressures. It as observed that ostial obstruction caused by se etion disappeared when the secretion as removed by sucking through the troc

I the sinusitis and control se ies f the present study ostial paten y as tested in three phases t the same examination: natively, post uctionally and post-irr gationally. The latter measurement as pe formed after careful removal by suction t the rr g tion fluid and possible ecretion. Observations made in the ous phase of examinati were best suited for ompa ison and results re most representati t ostial patency as tested post uctionally nd ostial penetrance for sniffing and bl ing postirrigationally. The difference t t een results f patency and penet ance testing is due to the different pressures used in testing ostial patency and penetrance.

Ostial respiratory obstruction is due either t the elling f mucosa and/or to secretion in the tubing or ostial canal. The respiratory p ten y t st takes both possibilities into onsiderat on simultaneously. The use of sniff/blow pressures as t decisi i fluenc m ki ng ses of the obstruction. olles muco membrane an be nsidered cause f ostial obstruction, f sniff/blow pressures must be ecorded inside the sinus. It is f rther possible that ostial obstruction is caused by secretion, even though no antral sniff/blow pressures can be recorded.

Ostial obstruction caused by mucous membrane s elling nd secretion occurred in present study in 40.8 % and obstruction caused by mucous membrane s elling only in 1 .5 %.

Disturbances of patency such as alve phenomenon and delayed return of pressure in the penetran test after sniffing and blowing, are interpreted only as signs f secretion.

When the ostial resistance was measured before the sinus secretion had been irrigated w y the united resistanc of the ostium and the secretion was recorded. A more representati result fo the ostial resistance only was obtained when resistance was measured after irrigation. In present sinusitis series, resistance was normal, 0—5 mm Hg, before irrigation in 53.1 % and fter irrigation in 71.2 %.

2. *Ostial pat ncy in sinusitis*

According to Drettner (1965c) an ostial obstruction for respiration is present in acute maxillary sinusitis in 68 % and fo sniffing and blowing, here indicated by the term penetrance, in every other case. In this series, the corresponding figures ere 32.8 % and 17.5 % taking the best patency f the three phases f the examination and the penetrance after the irrigation into account.

A valv phenomenon delayed return in the penetrance test oc urred in 59.4 % f these ses f the present sinusitis series in which the ostium as obstructed for quiet respiration. The val e occurred in this series tw ce as ften as in that of Drettner (1965c).

The discrepancies between results of the series f Drettner and f present study are apparently due to diff rent methods f investigation, diff rent evaluation f results and also differences in the series. In the present study ostial patency was examined only in reversibl cases of acute maxillary sinusitis. Furthe the details of the examination, the exact phase nd relation t irrigation and trials to eliminate the effect of secretion were not gi en in Drett ner' series. The most important reason f the differences between Drettner' and the present results is presumably secretion, to which pecial attention has been paid i this study.

Kerekes (1934) was the first to point out that ostial patency becomes normal as soon as sinusitis is cured, which is confirmed by the present study. A respiratory ostial obstruction was present at diagnostic puncture in 56.8 % and at the end of treatment in 12.7 %, which corresponds to the result in the control series. There was no sniff/blow penetrance at diagnostic puncture in every fourth case and at the end of treatment in 5.6 % of the cases.

The effect of sniff/blow on the ostial patency corresponded to Drettner's earlier observations, according to which an opening effect occurred in every fourth case when the ostium was obstructed. The fact that also the opposite obstructive effect occurred on sniffing and blowing in 2.0 % of the cases can be explained through movements of the secretion obstructing either the ostium or the trocar.

E. Ostial resistance in sinusitis

According to the investigations of Drettner (1965a) and Zippel & Meier (1968) the ostial resistance is normal, 10—25 mm H_2O, in every second case in maxillary sinusitis. The same result was obtained in the present study when the united resistance of the ostium and secretion was measured, i.e. the recordings were performed before irrigation.

Five mm Hg was taken as the upper limit of normal resistance in the present study. This value was taken from the results obtained in the control series and is only one fourth of what had been used in the above-mentioned investigations.

When resistance was measured after irrigation it was normal in maxillary sinusitis in 71.. %. Drettner's observation, that the return to normal of resistance takes place as soon as the sinusitis is cured, was confirmed by this study, in which resistance was elevated at diagnostic puncture in every second case and at the end of treatment in 5.1 % of the cases. In the present writer's opinion, return to normal resistance is due to decreased inflammatory swelling in the ostial mucosa during recovery.

Ostial obstruction has been considered the reason for retention of secretion inside the sinus (e.g. Naumann, 1965). In the writer's opinion, ostial obstruction is rather a result of the inflammatory process on the mucosa. This opinion is supported by the fact that a patent ostium is frequently found in cases of sinusitis even with abundant secretion in the sinus.

Consequently the greatest significance of ostial patency tests is, that they allow alterations in ostial patency to be observed during infection. When the ostium remains obstructed for several weeks in spite of therapy an irreversible inflammation is obvious.

By using ostial resistance measurement, information can be gained about ostial function. However the exactness of results of ostial patency tests makes these preferable to resistance measurement in spite of the following advantages of resistance measurement: uncomplicated equipment, ease of measurement and absence of sources of error. Resistance measurements cannot replace patency tests, but they offer some additional information as to ostial function and degree of ostial obstruction.

XI Summary

The present study consisting of 118 maxillary sinusitis cases, of such a degree of cateness that there was retention of secretion inside the sinus, the bacteriological findings corresponded to those of earlier investigations.

It was observed that there was no relation between ache and ostial patency or resistance. Furthermore, time of recovery from sinusitis was independent of whether ache was present at the beginning of infection or not.

At the X-ray examination, which was performed immediately before diagnostic puncture, the occipitofrontal, occipitomental and lateral projections were used. The findings were defined as follows: normal, slightly or markedly thickened mucosa, fluid level inside the sinus and homogeneously clouded sinus. When the mucosa was markedly thickened or the sinus homogeneously clouded, ostial obstruction was more common than in cases in which the mucosa was slightly thickened or there was fluid level inside the sinus. No correlation was observed between X-ray findings and ostial resistance.

Ostial patency was determined by comparing pressure variation in the nasopharynx, measured by anterior rhinomanometry and in the maxillary sinus, measured through a trocar. The measurements were performed consecutively on the sinus and the nasopharynx, and peak values during inspiration were evaluated. Because of natural variation of these values, the ostium was considered open when the peak of antral pressure decreases during inspiration were at least 75 % of the corresponding inspiratory pressure decreases in the nasopharynx. The suitability of this evaluation was proved by statistical analyses of the material.

Ostial patency and penetrance were tested in three phases of the same examination, namely postemotionally and postirrigationally. Optimal information about ostial patency was gained when the most normal patency was taken into account. When ostial patency and penetrance were tested in only one phase of the same examination, the patency was most often normal postemotionally and the sniff/blow penetrance postirrigationally.

Ostial respiratory obstruction is due to the swelling of mucosa and/or to secretion in the ostial canal. When the ostial sniff/blow penetrance is tested, ostial patency caused by mucous membrane swelling can be differentiated from that caused by secretion.

Ostial resistance was measured before and after irrigation. When resistance was measured before irrigation, the united resistance of ostium and secretion was recorded. A more reliable result about the ostial resistance was obtained when resistance was measured after irrigation.

In the sinusitis series, ostial patency tests and resistance measurements were repeated weekly until recovery. The ostium was found to be obstructed for respiration at diagnostic puncture in 50.8 % and at the end of treatment in 12.7 %, corresponding to that in healthy test subjects. The frequencies of open, partially open and obstructed ostia did not differ significantly when there was secretion inside the sinus.

There was no ostial sniff/blow penetrance in 26.7 % at diagnostic puncture and in 5.5 % at the end of treatment. A valve phenomenon (delayed pressure return after sniffing and blowing, probably caused by secretion, occurred in 50.4 % of ostia obstructed for respiration. The effect of sniff/blow on ostial respiratory patency was observed in 6.2 %.

In present study it was observed that the return to normal of ostial resistance took place as soon as the sinusitis was cured. At diagnostic puncture, resistance was elevated in 50.9 % and at the end of treatment in 5.1 %.

Kercher (1934) was the first to point out that ostial patency becomes normal as soon as sinusitis is cured, which is confirmed by the present study. A respiratory ostial obstruction was present at diagnostic puncture in 56.8 % and at the end of treatment in 1[illegible].7 % which corresponds to the result in the control series. There was no sniff/blow penetrance at diagnostic puncture in every fourth case and at the end of treatment in 6.6 % of the cases.

The effect of sniff/blow on the ostial patency corresponded to Drettner's earlier observations, according to which an opening effect occurred in every fourth case when the ostium was obstructed. The fact that also the opposite obstructive effect occurred on sniffing and blowing in [illegible]0 % of the cases can be explained through movements of the secretion obstructing either the ostium or the trocar.

E. Ostial resistance in sinusitis

According to the investigations of Drettner (1965a) and Zippel & Meier (1968) the ostial resistance is normal, 10—[illegible]5 mm H_2O in every second case in maxillary sinusitis. The same result was obtained in the present study when the united resistance of the ostium and secretion was measured i.e. the recordings were performed before irrigation.

Five mm Hg was taken as the upper limit of normal resistance in the present study. This value was taken from the results obtained in the control series and is only one fourth of what had been used in the above-mentioned investigations.

When resistance was measured after irrigation, it was normal in maxillary sinusitis in 71.2 %. Drettner's observation, that the return to normal of resistance takes place as soon as the sinusitis is cured, was confirmed by this study in which resistance was elevated at diagnostic puncture in every second case and at the end of treatment in 5.1 % of the cases. In the present writer's opinion, return to normal resistance is due to decreased inflammatory swelling in the ostial mucosa during recovery.

Ostial obstruction has been considered the reason for retention of secretion inside the sinus (e.g. Naumann 1965). In the writer's opinion, ostial obstruction is rather a result of the inflammatory process on the mucosa. This opinion is supported by the fact that a patent ostium is frequently found in cases of sinusitis even with abundant secretion in the sinus.

Consequently the greatest significance of ostial patency tests is, that they allow alterations in ostial patency to be observed during infection. When the ostium remains obstructed for several weeks in spite of therapy an irreversible inflammation is obvious.

By using ostial resistance measurement information can be gained about ostial function. However the exactness of results of ostial patency tests makes these preferable to resistance measurement in spite of the following advantages of resistance measurement: uncomplicated equipment, ease of measurement and absence of sources of error. Resistance measurements cannot replace patency tests, but they offer some additional information as to ostial function and degree of ostial obstruction.

VI Summary

The present study consisting of 119 maxillary sinusitis cases, of such degree of acuteness that there was retention of secretion inside the sinus, the bacteriological findings corresponded to those of earlier investigations.

It was observed that there was no relation between ache and ostial patency or resistance. Furthermore, time of recovery from sinusitis was independent of whether ache was present at the beginning of infection or not.

At the x-ray examination, which was performed immediately before diagnostic puncture, the occipitofrontal, occipitomental and lateral projections were used. The findings were defined as follows: normal, slightly or markedly thickened mucosa, fluid level inside the sinus and homogeneously clouded sinus. When the mucosa was markedly thickened or the sinus homogeneously clouded, ostial obstruction was more common than in cases in which the mucosa was slightly thickened or there was fluid level inside the sinus. No correlation was observed between x-ray findings and ostial resistance.

Ostial patency was determined by comparing pressure variation in the nasopharynx, measured by anterior rhinomanometry, and in the maxillary sinus measured through a trocar. The measurements were performed simultaneously on the sinus and the nasopharynx, and peak slopes during inspiration were evaluated. Because of natural variation of these, the ostium was considered open when the peaks of antral pressure decreases during inspiration were at least 75 % of the corresponding inspiratory pressure decreases in the nasopharynx. The suitability of this evaluation was proved by statistical analysis of the variation.

Ostial patency and penetrance were tested in three phases of the same examination: native, postsuctionally and postirrigationally. Optimal information about ostial patency was gained when the most normal patency was taken into account. When ostial patency and penetrance were tested in only one phase of the same examination, the patency was most often normal postsuctionally and the sniff/blow penetrance postirrigationally.

Ostial respiratory obstruction is due to the swelling of mucosa and/or to secretion in the ostial canal. When the ostial sniff/blow penetrance is tested, ostial patency caused by mucous membrane swelling can be *differentiated from* that caused by secretion.

Ostial resistance was measured before and after irrigation. When resistance was measured before irrigation, the united resistance of ostium and secretion was recorded. A more reliable result about the ostial resistance was obtained when resistance was measured after irrigation.

In the sinusitis series, ostial patency tests and resistance measurements were repeated weekly until recovery. The ostium was found to be obstructed for respiration at diagnostic puncture in 44.0 % and at the end of treatment in 14.7 % corresponding to that in healthy test subjects. The frequencies of open, partially open and obstructed ostia did not differ significantly when there was secretion inside the sinus.

There was no ostial sniff/blow penetrance in 26.7 % at diagnostic puncture and in 5.5 % at the end of treatment. A valve phenomenon or delayed pressure return after sniffing and blowing, probably caused by secretion, occurred in 50.4 % of ostia obstructed for respiration. The effect of sniff/blow on ostial respiratory patency was observed in 8.2 %.

In present study it was observed that the return to normal of ostial resistance took place as soon as the sinusitis was cured. At diagnostic puncture, resistance was elevated in 50.9 % and at the end of treatment in 5.1 %.

Kerekes (1934) was the first to point out that ostial patency becomes normal as soon as sinusitis is cured, which is confirmed by the present study. A respiratory ostial obstruction was present at diagnostic puncture in 50.8 % and at the end of treatment in 12.7 %, which corresponds to the result in the control series. There was no sniff/blow penetrance at diagnostic puncture in every fourth case and at the end of treatment in 5.5 % of the cases.

The effect of sniff/blow on the ostial patency corresponded to Drettner's earlier observations, according to which an opening effect occurred in every fourth case when the ostium was obstructed. The fact that also the opposite obstructive effect occurred on sniffing and blowing in 2.6 % of the cases can be explained through movements of the secretion obstructing either the ostium or the trocar.

E. Ostial resistance in sinusitis

According to the investigations of Drettner (1965a) and Zippel & Meier (1968) the ostial resistance is normal (0—25 mm H_2O) in every second case in maxillary sinusitis. The same result was obtained in the present study when the united resistance of the ostium and secretion was measured, i.e. the recordings were performed before irrigation.

Five mm Hg was taken as the upper limit of normal resistance in the present study. This value was taken from the results obtained in the control series and is only one fourth of what had been used in the above-mentioned investigations.

When resistance was measured after irrigation it was normal in maxillary sinusitis in 71.2 %. Drettner's observation that the return to normal of resistance takes place as soon as the sinusitis is cured, was confirmed by this study, in which resistance was elevated at diagnostic puncture in every second case and at the end of treatment in 5.1 % of the cases. In the present writer's opinion, return to normal resistance is due to decreased inflammatory swelling in the ostial mucosa during recovery.

Ostial obstruction has been considered the reason for retention of secretion inside the sinus (e.g. Naumann 1965). In the writer's opinion, ostial obstruction is rather a result of the inflammatory process on the mucosa. This opinion is supported by the fact that a patent ostium is frequently found in cases of sinusitis even with abundant secretion in the sinus.

Consequently, the greatest significance of ostial patency tests is, that they allow alterations in ostial patency to be observed during infection. When the ostium remains obstructed for several weeks in spite of therapy, an irreversible inflammation is obvious.

By using ostial resistance measurement, information can be gained about ostial function. However, the exactness of results of ostial patency tests makes these preferable to resistance measurement in spite of the following advantages of resistance measurement: uncomplicated equipment, ease of measurement and absence of sources of error. Resistance measurements cannot replace patency tests, but they offer some additional information as to ostial function and degree of ostial obstruction.

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SUPPLEMENT 329

NASOPHARYNGITIS

BY

SINSAK HORIGUTI

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ACTA OTO-LARYNGOLOGICA

SUPPLEMENT 329

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and Its Influence on General Diseases

——as the inflammatory source of focal infections, autoimmune and collagen diseases.
——as the trigger for the allergy
——as an origin of the autonomic nervous disorders through the continuous stimulation of respiration over the inflammatory surface of nasopharynx.

These facts are certified by the local treatment of this inflammation.

SINSAR HORIGUTI M. D

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Co-workers

K. Hamaguchi

K. Yamashita

Y. Saito

K. Yamada

C. Okubo

H. Furuya

M. Hasegawa

J. Okubo

Y. Ide

Y. Tanikawa

S. Tanaka

I. Shiose

A. Murakami

S. Katori

K. Bohno

S. Takeoda

M. Ichikawa

S. Harada

H. Ichikawa

S. Takayama

K. Fujimori

T. Takahashi

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Part I

Basic Study of Nasopharyngitis

1 Introduction

Nasopharyngitis, a peculiar diagnosis, should be news to the readers. This term probably cannot be found i any textbook of medicine, any reference book of otorhinolaryngology or in any literature hitherto published. Nasopharyngitis, the main subject of my lifework, is still an unknown problem of the medical world, as it were, a desert island in the sea however this desert island is really a treasury of medical science, the development of which may suggest the possibility of doing scientific reevaluation of not a little part of the acquired knowledge of medicine. The nasopharynx is, as will be stated in the following, an entrance, through which bacterial organism first gain entrance into the body and most people probably have a standing process of inflammation in this part of the body The most definite of the acute symptoms of such inflammation is the "common cold" and examination has proved the standing process of chronic inflammation to be a cause of allergy collagen diseases, diseases of the autonomic nervous system and various other diseases derived therefrom. For clarifying the mechanisms such as antibody production, fibrinolysis, pituitary-adrenal system, autonomic nervous mechanism, etc., which are supposed to be recovery mechanisms of the body the concept of nasopharyngitis will make an epoch and secondarily influence the interpretation of pathological mechanisms or the therapy of various diseases. From the standpoint nasopharyngitis many useless studies have been attempted in the present medical world.

The fact that such an important but single inflammatory focus has remained up to the present unnoticed by the medical eye, is astounding however a reason for this is that there are few local symptoms referable to nasopharyngitis. Since no local symptoms are presented from the beginning, the patients do not make any complaints, so that the physicians have likely had no opportunity of making these patients a subject of study

Another reason lies in the fact that the inflammation n this part displays only a few objective signs therefore, only redness is to be found even by an accurate observation with nasopharyngoscope or posterior rhinoscopy so that it will occasionally be overlooked. My study begins with the microscopic observation of the smears prepared by swabs obtained from the mucosa, for only in this way the existence of nasopharyngitis can be confirmed. My study is briefly outlined in due order in what follows.

Part II Clinical Aspects of Nasophryngitis

Part I

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2 Anatomy of the Nasopharynx

The nasopharynx is an elongated space extending posteriorly from the nasal cavities. The junction between the nasal cavities and the nasopharyngeal cavity corresponds to the choanae the posterior openings *of the nasal fossae*, closely adjacent to the posterior end of the nasal septum

The nasal septum is united with the hard palate, while the base of the nasopharynx is found by the so-called soft palate a non-osseous *part of the palate.* The nasopharynx is, therefore the space at the back of the soft palate, and its base is *formed by the soft palate itself.* The posterior wall of the nasopharynx is the frequent site of adenoid growth in the pharyngeal tonsils, and the bilateral pharyngeal openings of the auditory tube open on its lateral walls (Fig 1)

The epithelial cells lining the nasopharyngeal cavity are ciliated and columnar in shape. It is just the same with the mucosal epithelium

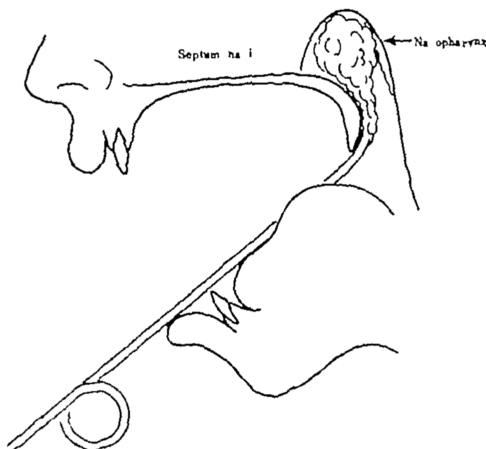


Fig 1 The Abrasion of the Nasopharynx

For the diagnosis and treatment of the nasopharyngitis and the nasopharynx stimulation for the observation of general reactions, this procedure is always performed. The abrasion of the nasopharynx is the preceding act to realize the study of all subjects described in this paper

For the treatment 1 ZnCl solution or other slight corrosive materials with some anesthetic are applied and at the same time the same abrasion is given from the nasal side with nasal cotton applicator to complete the treatment.

of the nasal cavities, larynx, trachea, etc. and is entirely different from that of the other parts of the pharynx, i.e. of the meso- and hypopharynx. In other words, the epithelial cells of the meso- and hypopharynx, in contrast to those of the nasopharynx, are a stratified, squamous nature. By reason of this fact it is indeed wrong to designate the nasopharynx as an epipharynx forming one part of the pharynx. The nasopharynx should be considered as one organ composing a part of the respiratory tract just as the nasal cavity larynx or trachea.

3 Physiology of the Nasopharynx

The nasopharynx differs not only in its structure from the other parts of the pharynx, as mentioned in the preceding paragraph, but also in its function. The role of the pharynx, namely is the downward transportation of food substances in contact with its surface however the nasopharynx does not play such a role. The food particles do not slide upon the nasopharyngeal surface. It is only the air of respiration that touches the nasopharynx on its surface.

The irritation of the nasopharynx, as stated in the following can produce reflex actions with decided significance to the organism but little is usually known about the matter. It should also be emphasized here that the reflex actions of the nasopharynx also differ widely from those of the pharynx. Namely the reflex actions of the pharynx are the so-called vomiting actions, whereas those of the nasopharynx are not vomiting but sneezing actions, as caused by irritation for instance, of the nasal mucosa. The nasopharynx therefore differs widely from the pharynx not only in morphological structure of the epithelium but also in physiological actions.

he air inhaled through the nostrils, as stated the preceding paragraph, arrives at the naso-arynx via the choanae, at which the current bent downward, and flows into the larynx and achea. The air flowing out through bilateral arrow nasal cavities abruptly into the naso-harynx becomes turbulent and will be drawn rther downward along the nasopharyngeal all, especially its bottom, the dorsal surface of he soft palate however on this occasion most f the dust particles in the ai with their bacteria ttach themselves to the nasopharyngeal wall, nd stimulate its mucosal surface physically as vell as chemically so that interruption of the illary motion of mucosal epithelium, invasion of dust particles into the mucosa, inflammation, acterial infections, etc. take place. As long as man breathes through the nose, those stimula-tions will always be present, so the practical features of the thus occurring nasopharyngitis should be described.

1) Nasopharyngitis in Autopsy Cases

To study the practical state of nasopharyngeal infections, the soft palate of 191 cadavers of various age was examined histopathologically (TAKAHASHI, 1973) Only those subjects were carefully selected and studied, in which clinic ally no oto-rhino-pharyngo-laryngological find-ings had been obtained the number of these cadavers of each age group is given in Table 1

Table 1 Number of subjects of histological observations of nasopharynx

New born–1 mon.		30 cases
1 mon.	1 y	19
1	10 y	18
10	20 y	15
20	30 y	20
30	40 y	10
40	50 y	23
50	60 y	19
60	70 y	20
70	85 y	17
total		191

In these cadavers inflammatory lesions on the dorsal surface of the soft palate were examined marked inflammatory changes were found even in the nasopharyngeal mucosa of a newborn infant which died 12 hours after birth.

About the dorsal surface of the soft palate of the cadavers, especially of newborn infants and of infants aged less than 1 month, an inflam-mation (chiefly cell infiltration, etc. in histology) rate of 76%, i.e. 23 out of 30 cases, was found, and the appearance rate of leucocytes was 78 %. The appearance rate of leucocytes, therefore, runs almost in parallel with the histological aspects of inflammation. In such an early period of life, however the inflammation itself in each individual case was not always con-spicuous. There were indeed exceptions, in which marked inflammatory lesions with leuco-cytic emigration through the epithelium and its desquamation were observed.

As reasons for the fact that the inflammation of the nasopharynx is variably intense t its primary infec tion, though they are not entirely known, various factors are considered, such as toxicity of bacteria, sensitivity of the individuals, etc. The effects of the inflammation on the whole body however for several reasons as will be mentioned later should differ in relation to the intensity of the inflammation itself. So-called exudative diathesis or asthenic constitution from infancy would seem to appear in such individuals as are profoundly influenced by primary infection. One of the most important factors determining the intensity of infections would possibly be the period of its onset, i.e. whether the infection occurs early or late in infancy. W intend to make study of the reactions in response to in-fections, by exposing germ-free animals at various stages to the external world.

In individuals of from 1 to 10 years of age the histological inflammation rate was 83% where-as the appearance rate of leucocytes was much decreased, to as little as 16 %. The incidence of nasopharyngeal infection increases gradually after birth, and in the histological features of infants over 1 year of age lymphocytes and

plasma cells begin to increase and leucocytes to decrease Thus the inflammation after the primary infection progresses gradually into the *chronic stage*.

This tendency of events grows further with age and at least over 25 years of age the appearance rate of leucocytes decreases further with increasing inflammation rate to the contrary and about from this period Russell's bodies appear beneath the epithelium (5–10%) and remain till an advanced age. Between 20 and 30 years of age the rate of inflammation and appearance of leucocytes is 90 % and 30 % (6 out of 20 cases) respectively which respectively further increases and decreases between 40 and 50 years of age Between 50 and 60 years of age inflammation occurs and leucocytes appear in 95 % and 11 respectively but between 70 and 85 years of age the rate of pathological inflammation and appearance of leucocytes is 95 % and 31 % respectively

From these observations no definite tendency in the appearance rate of leucocytes was to be found however the inflammation itself becomes increasingly intense with age, so that this indicates considering the personal history throughout the life that at least the majority of persons are now suffering or once suffered from nasopharyngitis.

No definite tendency was found in relation to the appearance rate of leucocytes and age because as factors causing acute exacerbation of inflammation not only age alone but also various other factors should be considered, such as air contamination etc We carried out for instance, a study on the state of the nasopharynx of laryngectomized and tracheotomized patients, a possible key also to the study of the air contamination and the results obtained are as follows. In these patients the possibility of postoperative infections does not need to be taken into consideration for the air does not flow through the nasopharynx during respiration

2) Course of Nasopharyngitis in Laryngectomized and Tracheotomized Patients

The subjects of the experiment were as given in Table 2 seven laryngectomized and 2 tracheotomized individuals hence 9 cases in all In

Table 2 Cases of laryngectomy and tracheotomy

Case No.	Age	Sex	Chief complaint	Diagnosis	Operation
1	73	M	hoarseness	laryngeal ca.	laryngectomy
2	62	M	hoarseness	laryngeal ca.	laryngectomy
3	58	M	dyspnoe	laryngeal ca.	laryngectomy
4	47	M	dyspnoe	laryngeal ca.	laryngectomy
5	49	M	dyspnoe	laryngeal ca.	laryngectomy
6	64	M	hoarseness	laryngeal ca.	laryngectomy
	63	F	dyspnoe	laryngeal ca.	laryngectomy
8	53	F	hoarseness	laryngeal mycosis	tracheotomy
9	66	M	hoarseness	laryngeal ca.	tracheotomy

each case cytological examination and bacteriological streaking with identification were done on the materials from the nasopharynx before operation

Case
Y H. 58y M. Laryngectomy due to Laryngeal Carcinoma.
In this case the exfoliation of epithelial cells from the nasopharynx was marked prior to operation, but decreased rather soon after operation. The wandering cells, though they were not so numerous from the beginning, disappeared completely 3 months later (Fig 2) Slight nasopharyngeal hemorrhages due to streaking (existence of slight erosion is considered) also disappeared soon. Before operation a moderate content of staphylococci and gramnegative bacilli was found however about 3 months later staphylococci and bacilli gradually decreased in number and disappeared.

As stated above the inflammatory state of the nasopharynx will gradually be improved by laryngectomy or tracheotomy however the progress of the improvement is extremely slow and differs widely from that caused by local treatment From the above we know that the healing of the inflammation is interrupted by constant irritation due to the flow of (contaminated) respiratory air through the nasopharynx, and on the contrary the inflammation will improve spontaneously if the respiratory air does not flow through

3) Nasopharyngeal Infections of the New born Infants

The period of the primary occurrence of infections in the nasopharyngeal mucosa of the neonatal infant is a matter of particular interest This region is probably the primary site of air borne infections deep in the organism. Sirosc (1968) in our clinic examined in detail

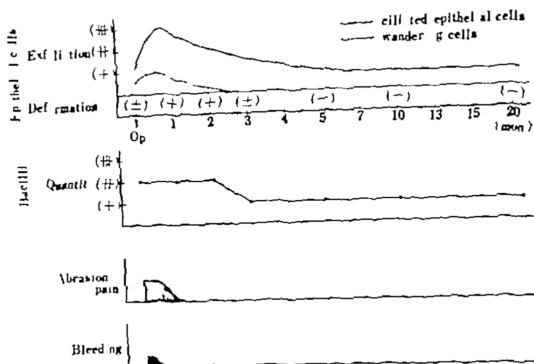


Fig. 2. Course of nasopharyngitis of patient with laryngeal carcinoma (Y.H. 56y. M.)

Table 3. Comparison of nasopharyngeal cytology before and after laryngectomy and tracheostomy

Case No.	observation period	before operation: ciliated cells: desquamation	before operation: ciliated cells: deformation	before operation: wandering cell	after operation: ciliated cells: desquamation	after operation: ciliated cells: deformation	after operation: wandering cells
1	24 mon	++	+	+	+	±	±
2	6 mon	±	+	+	−	−	−
3	22 mon	+	±	±	+	−	−
4	20 mon	+	±	+	+	−	±
5	20 mon	+	++	++	+	±	±
6	18 mon	+	±	±	±	−	−
7	12 mon	+	+	++	+	−	±
8	25 mon	++	+	++	+	∓	∓
9	5 mon	+	++	++	+	+	++

Table 4. Comparison of nasopharyngeal bacterial flora before and after laryngectomy and tracheostomy

Case No.	observation period	before operation: bacterial content	before operation: bacterial species	after operation: bacterial content	after operation: bacterial species
3	22 mon	++	non-hemolytic staphyl.	+	non-hemolytic staphyl.
4	20 mon	+++	non-hemolytic staphyl. G(−)	+	staphyl.
5	20 mon	+++	staphyl. G(−)	+	staphyl.
7	12 mon	+++	non-hemolytic staphyl.	+	staphyl.
8	23 mon	++	staphyl.	+	staphyl.
9	mon	+++	hemolytic staphyl.	+	hemolytic staphyl.

plasma cells begin to increase and leucocytes to decrease. Thus the inflammation after the primary infection progresses gradually into the chronic stage

This tendency of events grows further with age and at least over 25 years of age the appearance rate of leucocytes decreases further with increasing inflammation rate to the contrary and about from this period Russell's bodies appear beneath the epithelium (5–10 %) and remain till an advanced age. Between 20 and 30 years of age the rate of inflammation and appearance of leucocytes is 90 % and 30 % (6 out of 20 cases) respectively which respectively further increases and decreases between 40 and 50 years of age. Between 50 and 60 years of age inflammation occurs and leucocytes appear in 95 % and 11% respectively but between 70 and 85 years of age the rate of pathological inflammation and appearance of leucocytes is 95 % and 31% respectively

From these observations no definite tendency in the appearance rate of leucocytes was to be found however the inflammation itself becomes increasingly intense with age, so that this indicates, considering the personal history throughout the life that at least the majority of persons are now suffering or once suffered from nasopharyngitis

No definite tendency was found in relation to the appearance rate of leucocytes and age, because as factors causing acute exacerbation of inflammation not only age alone but also various other factors should be considered such as air contamination etc We carried out for instance a study on the state of the nasopharynx of laryngectomized and tracheotomized patients, a possible key also to the study of the air contamination and the results obtained are as follows In these patients the possibility of postoperative infections does not need to be taken into consideration for the air does not flow through the nasopharynx during respiration

2) Course of Nasopharyngitis in Laryngectomized and Tracheotomized Patients

The subjects of the experiment were as given in Table 2 seven laryngectomized and 2 tracheotomized individuals hence 9 cases in all In

Table 2 Cases of laryngectomy and tracheotomy

Case No.	Age	Sex	Chief complaint	Diagnosis	Operation
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2	62	M	hoarseness	laryngeal ca.	laryngectomy
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Table 7 Nasopharyngeal bacterial flora of normal infant.

Micrococcus	72.5%	(87)
Staph. epidermidis	32.5	(39)
Staph. aureus	15.8	(19)
Str. viridans	10.0	(12)
Str. anhaemolyticus	8.3	(10)
Str. haemolyticus	5.0	(6)
Diplococcus	2.5	(3)
	120 cases	

Table 8 Staphylococcus in nasopharynx of normal children.

Coagulation of plasma	Fermentation of mannite	
+	+	32.8% (19)
+	−	0% (0)
	+	43.1% (25)
	−	24.1% (14)

Table 9 Nasopharyngeal bacterial flora in cases of nasopharyngitis.

Staph. epidermidis	45.4%	(98)
Staph. aureus	27.8	(60)
Macrococcus	14.4	(31)
Str. viridans	14.4	(31)
Str. anhaemolyticus	12.5	(27)
Str. haemolyticus	8.3	(18)
E. coli	3.7	(8)
Proteus vulgaris	3.2	(7)
Diplococcus	2.2	(5)
Neisseria	1.8	(4)
Candida	0.9	(2)
(−)	12.5	(27)
	216 cases	

Arakawa-ku, Tokyo and aged from 6 to 1 years, and the results obtained are given in Table 7

Of the flora detected those with apparent pathogenity are 15.8% staphylococcus aureus, 10.0% streptococcus viridans, 8.3% strept. anhaemolyticus, 5.0% strept. haemolyticus and 2.5 pneumococcus. Staph. epidermidis, together with staph. aureus, was classified, as shown in Table 8, according to the results of coagulase test and fermentation of mannite confirming pathogenicity and, in 32.8% of both strains of staphylococci both tests gave positive results.

From these results it has been amply demonstrated, that the bacterial flora fixed in the nasopharynx of children of various strains of bacteria were detected from each of all 120 children examined and it is characteristic of these strains that gram-positive micrococci, probably a kind of saprophytic organism in the nasopharynx, were found in 72.5% of the subjects.

This fact is interesting to us, as compared with the results of determination of bacterial flora, as shown in Table 9 for the adult nasopharynx. Namely in the nasopharynx of adults the gram-positive micrococci mentioned previously occur only in 14.4% of the cases, in a much smaller percentage than in infants. On the contrary staphylococci are notably growing with age, especially pathogenic staphylococcus aureus, from 15.8% in infants to 27.8 in adults. Furthermore, each of the pathogenic organisms of the other strains is also growing in adult cases, which fact may naturally be attributed to their long history.

5) Inflammation of the Nasopharynx with Rise and Fall of its Bacterial Content

The bacterial infections of the nasopharynx have been mentioned above. However it is natural that the bacterial flora is not always constant. In the case of the so-called "common cold" it will always be accompanied by an acute inflammation of the nasopharynx (I am of the opinion to the contrary that a cold should rather be defined as acute nasopharyngitis.) and the nasopharyngitis develops its local symptoms, which never become evident otherwise subjectively and especially the following symptoms become noticeable (it appears to be fairly well demonstrated that the symptoms in case of cold, such as headache, pyrexia, general feebleness, etc. are closely related with nasopharyngitis as well, and for further details, refer to respective paragraphs on headache and the autonomic nervous system)

1 Feeling of dryness on the dorsal surface of the nasopharynx. (This sensation is frequently complained of erroneously as an abnormal feeling in the pharyngo-laryngeal region.)

2 Open nasal voice (especially of [m n ŋ]) of slight degree, appearing in the earliest stage of a cold.

The nasopharyngitis, therefore, will be felt in the form of an acute exacerbation at least in case of a cold and furthermore, even at the end of the cold inflammation of the nasopharynx is

how the nasopharynx of neonatal infants gets involved with bacterial organisms, and also studied the inflammatory conditions of the nasopharynx of school children and adults.

A total of 100 newborn less than 14 days after birth (of which 86 were aged less than 7 days and thereafter more than 10 cases each respectively) subjects without any noticeable disease of the upper respiratory tract from the neonatal care unit of the maternity room of our university clinic, were examined for the presence of bacterial flora in the nasopharynx. For obtaining material to determine the bacterial flora a sterile cotton swab for nose, with its head bent at an angle of 90 was inserted carefully into the mouth using a tongue depressor to avoid contamination and the dorsal surface of the soft palate was gently scraped material so removed was spread rapidly and if necessary cultured by various cultural methods and studied for the presence of bacterial organisms. The results obtained are given in Table 5

As for the relationship between the lapse of time i e. days after birth and the detected bacterial flora staphylococcus epidermidis (non pathogenic) for instance was detected in 4 out of 14 cases of the newborn only one day after birth and the positive cases increased with

T ble 5 Day after birth nd numbe of cases w th positi e bacteria.

Days	1	2	3	4	5	6	7	8–14
Staph. epiderm.	4	5	7	9	11	13	6	12
Micrococcus				1		3	3	1
E. coli		1						2
Str anhaemol.					1			
Str viridans				1				
(−)	10	8	6	1				1
Cases	14	13	13	11	12	15	8	14

Table 6 Bacterial content (number of colonies on the plate)

(−)	no colony
(±)	1
(+)	a few scattered
(++)	moderate disseminated
(+++)	multiple densely packed

the course of time. In regard to the other bacterial organisms (except the cases of gram-positive ones) however they did not always increase in parallel with the days after birth. But the kinds of the detectable bacterial organisms increased gradually The number of bacterial colonies on a culture plate, as shown in Table 6 is as shown in Fig 3 from Table 5 At a glance it will be found that the number of bacteria adhering to the nasopharynx increases daily

Even with the superficial examination shown above streptococcus haemolyticus or streptococcus viridans are already found As already stated an infant which died 12 hours after birth has shown inflammation beginning on the dorsal surface (at the nasal side) of the soft palate and from the nasopharynx of an infant which visited our clinic 10 days after birth with otitis media, pathogenic organisms were found which were similar to those in otitis media So the infection of the nasopharynx by pathogenic organism occurs earlier than could be expected and therefore the occurrence of the inflammation in the nasopharynx, i e nasopharyngitis will presumably take palce shortly after birth

4) Nasopharyngitis of School Children and Adults

Shoas (1968) studied on the bacterial flora obtained from the nasopharynx in 120 random samples from primary school children living in

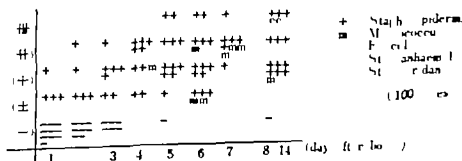


Fig 3. Day after birth and content of bacteria detected

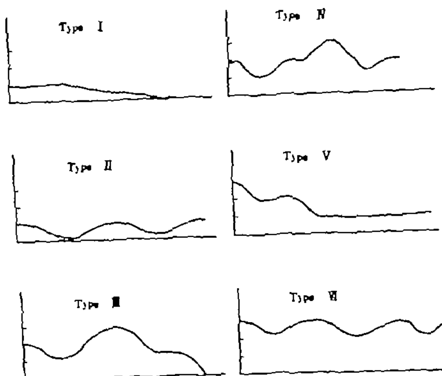


Fig. 4. Bacterial flora curv

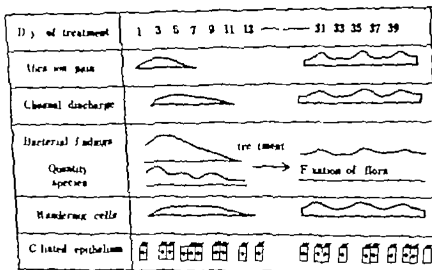


Fig. 5. Bacteriological state and nasopharyngeal findings during local treatment.

revealed by local examination though usually the patient is not conscious of it

The existence of nasopharyngitis as will be mentioned later is to be determined by

1 Amount of exfoliated epithelial cells
2 Appearance of wandering cells,
3 Bacterial content, etc.

In order to compare the bacterial content with the intensity of inflammation however it must be considered, whether or not a method for determination of inflammation exists, irrespective of bacterial content. In our clinic, as will be mentioned later various tests on animals and laboratory tests have revealed the existence of a close relationship between the amount of exfoliated epithelial cells or appearance of wandering cells and the intensity of inflammation and it has been also elucidated that clinically

1 the intensity of pain at and after abrasion of the nasopharyngeal mucosa and

2 the degree of mucosal hemorrhages (the extent of erosion) at and after abrasion

are closely related with the inflammation.

On the strength of these clinical data TANIKAWA has carried out a study of the correlations between the intensity of nasopharyngitis and bacterial flora (The traditional method of study i e. only the visual observation of the color tone (grade of redness) of the mucosa with a posterior rhinoscope etc. is not enough to determine the grade of nasopharyngitis. It can be shown by experiment that the above mentioned criteria such as abrasion pain postabrasive hemorrhages, etc. are much more reliable for this purpose)

TANIKAWA (1970) prepared nasopharyngeal abrasion specimens from patients with nasopharyngitis and normal subjects daily (abrasion culture from the dorsal surface of the soft palate by nasal as well as pharyngeal swabs) and followed the alteration of the bacterial flora in this region This observation was done naturally in parallel with the nasopharyngeal local treatment (application of 1 $ZnCl_2$) however in some cases it was found that the inflammation of the nasopharynx often recurs in spite of therapy In most of these cases, the feeling of dryness in the soft palate the open nasal voice such as found with a cold as mentioned above did not always appear but an acute exacerbation in the nasopharynx, if it ever appeared, almost always ceased within 1–2 days without any subjective symptoms.

The so-called cold therefore should be defined as an acute exacerbation of nasopharyngitis especially with more difinite local symptoms, and accompanied by generalized (acute) symptoms of the autonomic nervous system

By the daily examination of bacterial flora in the nasopharynx it was found that in the nasopharynx with acute symptoms (clinically best judged from the abrasion pain and postabrasive hemorrhages by swabs) regardless of whether the infection is latent or manifest both the quantity and the kind of bacterial organisms are increased

The bacteriological abrasive specimens obtained at the first medical examination from the nasopharynx previous to any treatment contain naturally various kinds of bacteria in large quantities however these organisms react diversely to local treatment (application of 1 $ZnCl_2$) for nasopharyngitis.

In some cases the bacterial flora is rapidly diminished by treatment and the patient recovers from the inflammation while in others the bacterial organisms resist the intensive treatment obstinately and never decrease so that the symptoms cannot improve TANIKAWA classified the clinical course of these bacterial organisms into 6 types as is given in Fig 4

- Type I — Slightly alterating bacterial flora with rapid disappearance of bacteria after treatment (15)
- Type II — Slightly alterating bacterial flora without disappearance of bacteria (24 %)
- Type III — Widely alterating bacterial flora with disappearance of bacteria (11)
- Type IV — Widely alterating bacteria flora without disappearance of bacteria (34)
- Type V — Widely alterating bacterial flora stabilized after prolonged treatment (5)
- Type VI — Many different kinds of bacteria in large quantities without disappearance even after prolonged treatment (1[illegible])

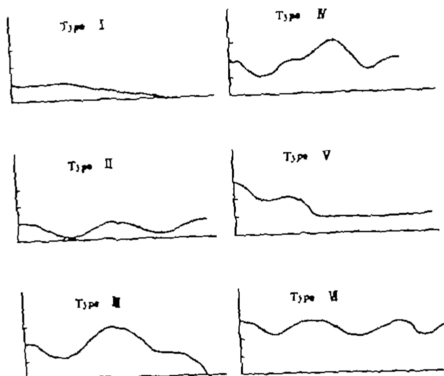


Fig. 4. Bacterial flora curve.

Days of treatment	1 3 5 7 9 11 13 —— —31 33 35 37 39
Vibration pain	
Choanal discharge	
Bacterial findings Quantity species	treatment ⟶ Fixation of flora
Wandering cells	
Ciliated epithelium	

Fig. 5. Bacteriological state and nasopharyngeal findings during local treatment.

During the course of treatment for nasopharyngitis with alterations in the bacterial flora however staphylococcus aureus is the most fundamental cause of the inflammation

In cases in which the inflammation becomes aggravated therefore staphylococcus aureus naturally increases and other bacteria causing acute inflammations such as streptococcus viridans streptococcus haemolyticus, streptococcus anhaemolyticus, pneumococcus, etc. make their appearance simultaneously In such cases, however only the staphylococcus remains alive generally while the inflammation disappears soon during local treatment. The bacteriological states in these cases are given in Fig 5

The alterations of the bacterial flora however depending also a little upon the techniques of local treatment etc. does not always go parallel with the alterations of the inflammation itself The bacterial flora curve described above should indicate for reference only the average data for the conditions. Further it is characteristic of nasopharyngitis as will be mentioned later that its treatment will also heal dysfunctions of the other distant organs or the whole body

If the inflammation in the nasopharyngeal region as its original point is refractory and persists, however no effects of treatment for the nasopharynx upon the whole body can be expected.

5 Inflammation of the Nasopharynx and Epithelial Changes

In the nasopharynx, as mentioned above latent inflammations exist constantly and recur repeatedly. Thereby it was stated that (1) the nasopharyngeal symptoms are mostly latent in themselves and (2) the diagnoses of these symptoms cannot always be entirely satisfactorily established by traditional oto-rhino-laryngological methods, i.e. visual methods such as pharyngoscopy or posterior rhinoscopy etc. To solve this 2nd diagnostic problem (which is, however, of decided importance in finding the inflammation, called nasopharyngitis) a method must be developed which is entirely different from the traditional ones.

As stated already in the preceding paragraph, abrasion pain, postabrasive hemorrhages, etc. are the clinical criteria for the diagnosis. However in establishing a reliable diagnosis, it is necessary to examine the abrasion specimen from the nasopharyngeal mucosa, because the abrasion pain is a more or less subjective criterion and the hemorrhages can be found only in case of rather severe inflammation with erosion.

In these cases observations of the pathological conditions of bacterial organisms and wandering cells were carried out, and the ciliated epithelium of the nasopharyngeal mucosa was also observed to show marked transformation and desquamation under inflammatory conditions. It has already been found by us at the beginning of the study on nasopharyngitis that in inflammatory conditions numerous epithelial cells are exfoliated and desquamated. Smeared specimens containing the nasopharyngeal epithelium were prepared by slight abrasion of the nasopharyngeal wall (chiefly the dorsal surface of the soft palate) with pharyngeal or nasal swabs and observed easily after Papanicolaou's staining, and the criteria for the correlation between the cytological features of desquamated epithelium and the process of inflammation had to be established. For this purpose the states of improvement and cellular exfoliation were successively recorded in the cases of artificially induced inflammation in the nasopharynx of animals (ICHIKAWA, 1964), the states of improvement and cellular exfoliation were observed during the treatment of nasopharyngitis of man (SAITO 1963) and the correlations between the abrasion pain or postabrasive hemorrhages and the inflammation were, as mentioned previously, exfoliative-cytologically observed (IDE, 1965a). In our clinic, however, prior to all these methods, MURAKAMI (1967) had performed a morphological study of the exfoliated epithelial cells in cases of nasopharyngitis and made its basis firm.

1) Morphology of the Nasopharyngeal Epithelial Cells

The epithelium of the nasopharynx is ciliated columnar as has been mentioned. Morphologically this is an epithelium of almost the same type as in the nasal cavities. In the other parts of the pharynx, i.e. meso- and hypopharynx, the epithelium is stratified squamous, and this layer will probably be related downward with the esophageal wall, however the nasopharyngeal mucosa is characterized only by a pure respiratory type of wall and is entirely different from the pharyngeal mucosa in its morphology.

A normal epithelial cell consists of cilia, cell body, cuticular border, nucleus and tail. According to the results of a morphological study on 100 ciliated epithelial cells obtained from the normal nasopharynx, MURAKAMI (1967) classified them into 4 types as shown in Fig. 6: Type-I, Type II, Type IIIA and Type-IIIB. Type-I, II and III correspond to the medium sized, elongated and shortened cells respectively; subdivision of the type III enables the separation especially of the shortest cells from the others in the same group. The cilia are about 8μ in length and adhere orderly in

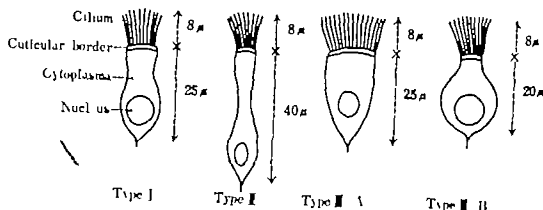


Fig 6. Types of normal ciliated epithelial cells obtained from the normal nasopharynx.

Table 10 Appearance rate of epithelial cells in normal condition.

cell type	ciliar type			
	I	II	III	total
normociliar	66%	8%	6%	80%
incomplet ciliar	4%	2%	1%	7%
aciliar	6%	4%	3%	13%

parallel with each other to the head of each cell In the boundary between its border and the cell body there is a *band shaped darkstaining* region called the cuticular border from which the cilia sprout The normal cilia grow as mentioned above in parallel and in the same length from the entire surface of the cuticular border but occasionally they are shortened frizzled or only half the size of normal ones and they even completely disappear as incomplete forms and the cuticular border which is clearly defined in normal cells becomes ill defined or even lost and invisible occasionally In the smears obtained from the clinically normal appearing nasopharynx the epithelial cells were of the so-called normal type i.e. I II and III as stated above of incompletely ciliated type and non-ciliated type in about 80 7 and 13 of all respectively with a scattering of goblet cells (MURAKAMI 1967)

2) Epithelial Cells in Inflammatory Conditions

Nasopharyngitis exists as stated in the preceding paragraph always latently and presents temporarily local symptoms such as a feeling of dryness on the dorsal surface of the soft palate open nasal voice of slight degree etc especially when having a cold When these transitory local symptoms appear it may be considered as acute nasopharyngitis or acute exacerbation of nasopharyngitis, whereas latent nasopharyngitis in general is to be regarded probably as subacute form of the disease. In the latter cases are included those occasionally in which posterior rhinorrhea is especially marked (even without evidence of sinusitis) but no abrasion pain and hemorrhages are found We regard such a form of the disease as chronic nasopharyngitis. The chronic nasopharyngitis is a *disease refractive* to therapy In the article presented by MURAKAMI (1967) the acute nasopharyngitis in this study corresponds to the acute nasopharyngitis as well as the acute exacerbation of chronic nasopharyngitis, and the subacute nasopharyngitis to the non-acute nasopharyngitis without posterior rhinorrhea. The chronic nasopharyngitis corresponds to that with posterior rhinorrhea previously mentioned In these cases however there can be found many cases with marked abrasion pain despite posterior rhinorrhea. Although such classification is, therefore also not always justified we have classified the disease at present into acute subactue and chronic type from 10 years clinical experience

Nasopharyngitis and Desquamation of Epithelium

The correlation between the grade of inflammation and desquamation of the epithelium or transformation of desquamated epithelial cells, as has been mentioned in the preceding paragraph should be stated here in detail There are two ways to observe inflammatory changes in epithelial cells. One is the examination of the desquamated epithelium in the smears from animals with artificially produced acute nasopharyngitis, compared with histopathological

features of the nasopharyngeal mucosa in its respective stage of the disease, and the other is the examination of smears during the recovery course of the patients under treatment. The significance of the desquamated epithelial cells can be exactly determined only by comparison of the results obtained in both these ways.

ICHIKAWA (1964) studied the desquamated epithelial cells of the nasopharynx of rabbits in comparison with the recovery process of its acute inflammation, which was induced by administration of 10% formol in the nasopharynx. This experiment corresponds indeed rather with successive observation of the recovery process of the nasopharyngeal mucosal lesions after instillation of formol, but is interesting in the respect that the possible correspondence of the cytological aspects of desquamated epithelium with the histological features of the mucosa itself within the first 24 hours was noticed, while the desquamated epithelial cells were compared with the mucosal tissue itself during the course 1, 3, 6, 12 and 24 hours and further 3, 7, 14 and 28 days after instillation.

The nasopharyngeal (of the dorsal surface of the soft palate) mucosa of rabbits before instillation of formol is, as shown in Fig. 7a, covered with ciliated epithelium and its smears (Fig. 7b) contain only ciliated epithelial cells. The cilia of the epithelial cells 1 hour after instillation of formol are, as given in Fig. 8a, irregularly concentrated and the intercellular spaces are slightly edematous. The lamina propria shows slight inflammatory edema and cellular infiltra-

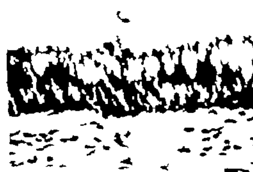


a. Nasopharyngeal mucosa of normal rabbit.



b. Ciliated epithelial cell from the nasopharynx of normal rabbit.

Fig. 7 Before instillation of formol.



a. Irregularly concentrated cilia slightly loose connected epithelial cells. Slight edema and cell infiltration in the stratum proprie.



b. Irregularly bundled cilia and irregularly attached ry taphases. Epithelial cells easily desquamated and disconnected.

Fig. 8. One hour after instillation

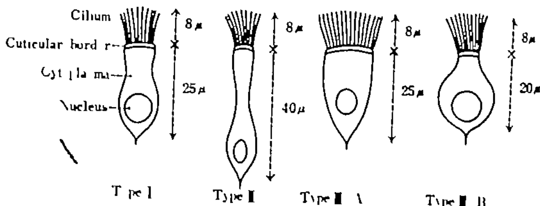


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Nasopharyngitis and Desquamation of Epithelium

The correlation between the grade of inflammation and desquamation of the epithelium or transformation of desquamated epithelial cells as has been mentioned in the preceding paragraph should be stated here in detail There are two ways to observe inflammatory changes in epithelial cells. One is the examination of the desquamated epithelium in the smears from animals with artificially produced acute nasopharyngitis, compared with histopathological

features of the nasopharyngeal mucosa in its respective stage of the disease, and the other is the examination of smears during the recovery course of the patients under treatment. The significance of the desquamated epithelial cells can be exactly determined only by comparison of the results obtained in both these ways.

ICHIKAWA (1964) studied the desquamated epithelial cells of the nasopharynx of rabbits in comparison with the recovery process of an acute inflammation, which was induced by administration of 10% formol in the nasopharynx. This experiment corresponds indeed rather with a successive observation of the recovery process of the nasopharyngeal mucosal lesions after instillation of formol, but is interesting in the respect that the possible correspondence of the cytological aspects of desquamated epithelium with the histological features of the mucosa itself within the first 24 hours was noticed while the desquamated epithelial cells were compared with the mucosal tissue itself during the course 1, 3, 6, 12 and 24 hours and further 3, 7, 14 and 28 days after instillation.

The nasopharyngeal (of the dorsal surface of the soft palate) mucosa of rabbits before instillation of formol is, as shown in Fig. 7a, covered with ciliated epithelium and its smears (Fig. 7b) contain only ciliated epithelial cells. The cilia of the epithelial cells 1 hour after instillation of formol are, as given in Fig. 8a, irregularly concentrated and the intercellular spaces are slightly edematous. The lamina propria shows slight inflammatory edema and cellular infiltra-



a. Nasopharyngeal mucosa of normal rabbit.



b. Ciliated epithelial cell from the nasopharynx of normal rabbit.

Fig. 7 Before instillation of formol.



a.
Irregularly concentrated cilia slightly loose connected epithelial cells. Slight edema and cell infiltration in the lamina propria.



b.
Irregularly bundled cilia and irregularly vacuolated cytoplasma. Epithelial cells easily desquamated and disconnected.

Fig. 8. One hour after instillation

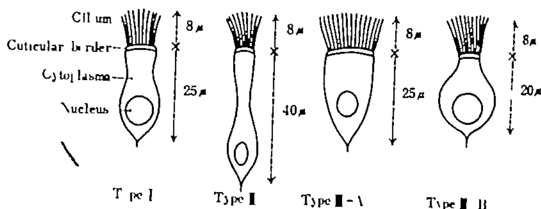


Fig. 6. Types of normal ciliated epithelial cells obtained from the normal nasopharynx.

Table 10 Appearance rate of epithelial cells in normal condition.

cell type	ciliar type			
	I	II	III	total
normociliar	66%	8%	6%	80%
incomplet ciliar	4%	2%	1	7%
acilia	6%	4%	3%	13%

parallel with each other to the head of each cell. In the boundary between its border and the cell body there is a band shaped darkstaining region called the cuticular border from which the cilia sprout The normal cilia grow as mentioned above in parallel and in the same length from the entire surface of the cuticular border but occasionally they are shortened frizzled or only half the size of normal ones and they even completely disappear as incomplete forms and the cuticular border which is clearly defined in normal cells, becomes ill defined or even lost and invisible occasionally In the smears obtained from the clinically normal appearing nasopharynx, the epithelial cells were of the so-called normal type i e. I II and III as stated above, of incompletely ciliated type and non-ciliated type in about 80, 7 and 13 of all respectively with a scattering of goblet cells (MURAKAMI 1967)

2) Epithelial Cells in Inflammatory Conditions

Nasopharyngitis exists, as stated in the preceding paragraph always latently and presents temporarily local symptoms such as a feeling of dryness on the dorsal surface of the soft palate, open nasal voice of slight degree etc. especially when having a cold When these transitory local symptoms appear it may be considered as acute nasopharyngitis or acute exacerbation of nasopharyngitis whereas latent nasopharyngitis in general is to be regarded probably as subacute form of the disease In the latter cases are included those occasionally in which posterior rhinorrhea is especially marked (even without evidence of sinusitis) but no abrasion pain and hemorrhages are found. We regard such a form of the disease as chronic nasopharyngitis. The chronic nasopharyngitis is a disease refractive to therapy In the article presented by MURAKAMI (1967) the acute nasopharyngitis in this study corresponds to the acute nasopharyngitis as well as the acute exacerbation of chronic nasopharyngitis, and the subacute nasopharyngitis to the non acute nasopharyngitis without posterior rhinorrhea. The chronic nasopharyngitis corresponds to that with posterior rhinorrhea previously mentioned In these cases, however there can be found many cases with marked abrasion pain despite posterior rhinorrhea. Although such classification is, therefore, also not always justified we have classified the disease at present into acute subactue and chronic type from 10 years clinical experience

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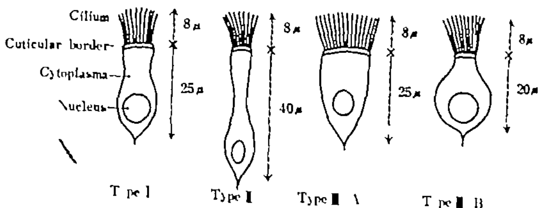


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a.

Superficial mucosal erosion or ulceration with beginning repithelization from the adjacent mucosa. In the stratum proprin vascular dilatation, edema and cellular infiltration are still found.



b.

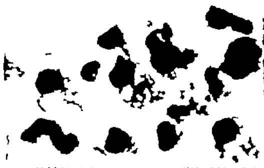
A few cells with distinct border and abundant chromatin.

Fig. 12. 3 days after Instillation



a.

Though repithelization is marked, still the epithelial cells are irregularly arranged. Ciliated cells or goblet cells are not formed yet. Capillarization and proliferation of fibroblast in the stratum proprin.



b.

Appearance of polyhedral or cylindrical epithelial cells with distinct border

Fig. 13. 7 days after Instillation.



a.

Advanced differentiation of the regenerated epithelium; the epithelial layer is nearly of normal structure.



b.

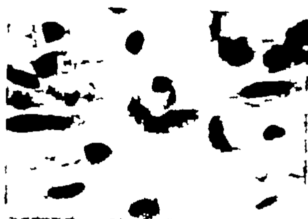
Appearance of ciliated cells of normal shape cylindrical and goblet cells are scattered.

Fig 14. 14 days after Instillation.



a.

Marked swelling of epithelial cell with decrease of intercellular connection occasional desquamation of epithelium and marked leucocytic infiltration. Marked hyperemia and edema in the stratum propria.



b.

Epithelial cells desquamated quite easily marked deformation of cell and degeneration of cytoplasma.

Fig 9 3 hours after instillation.



a.

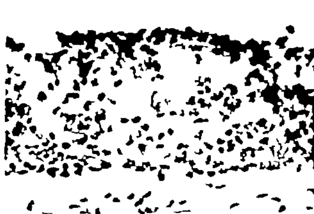
Destruction and desquamation of epithelial cells become marked on the basement membrane remain only the reserve cells. In the stratum propria vascular dilatation edema and cellular infiltration become marked.



b.

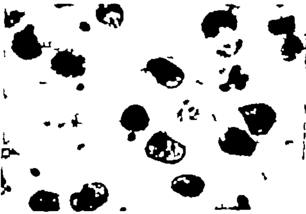
Cellular degeneration and deformation become marked loss of cilia, disintegration of cytoplasma nuclear swelling and karyorrhexis and pyknosis.

Fig 10. 6 hours after instillation.



a.

Epithelial cells are destructed and desquamated remaining reserve cells are only scattered, ulceration is found in certain areas with marked changes.



b.

Cells are destroyed only scattered cells with round or oval nuclei and obscure cytoplasma

Fig 11 24 hours after instillations.



a.

Superficial mucosal erosion or ulceration with beginning reepithelization from the adjacent mucosa. In the stratum propria vascular dilatation, edema and cellular infiltration are still found.



b.

A few cells with distinct border and abundant chromatin.

Fig. 12. 3 days after instillation



a.

Though reepithelization is marked, still the epithelial cells are irregularly arranged. Ciliated cells or goblet cells are not formed yet. Capillarization and proliferation of fibroblast in the stratum propria.



b.

Appearance of polyhedral or cylindrical epithelial cells with distinct border

Fig. 13. 7 days after instillation.



a.

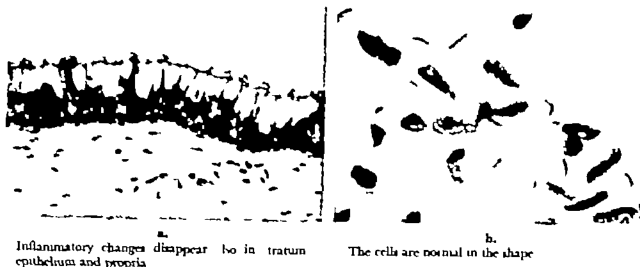
Advanced differentiation of the regenerated epithelium; the epithelial layer is nearly of normal structure.



b.

Appearance of ciliated cells of normal shape; cylindrical and goblet cells are scattered.

Fig. 14. 14 days after instillation.



a.
Inflammatory changes disappear also in stratum epithelium and propria

b.
The cells are normal in the shape

Fig 15. 28 days after instillation.

tion, and in the corresponding smears, as shown in Fig 8b the cilia are found in irregular bundles and the cells contain multiple vacuoles of varying size in the cytoplasm The epithelial cells then become easily desquamated The intercellular edema becomes marked three hours after instillation (Fig 9a) the epithelial cells are partly desquamated and leucocytic emigration through the loosening epithelial layer is found In the smears as seen in Fig 9b the epithelial cells become desquamated much more easily and the transformation of cells swelling and vacuolization of cytoplasma are conspicuous

Six hours later (Fig 10a) the epithelial layer is necrotized almost completely and only a few reserve cells are visible on the basement membrane In the lamina propria dilatation of blood vessels edema and cell infiltration are noted In the smears (Fig 10b) transformation and degeneration of the epithelial cells become conspicuous and irregularity of cilia loosening of cytoplasma swelling of nucleus, karyolysis etc are noted

In the histology 24 hours after instillation (Fig 11a) the normal structure of the epithelial layer disappears completely undergoes necrosis and single-layered reserve cells with pyknosis are found along the basement membrane In the smears (Fig 11b) the cytoplasma of the epithelial cells is destroyed and lost and only a few round or oval nuclei are scattered here and there

In the cases 3 days after instillation as seen in the histology (Fig 12a) the so-called ciliated epithelium of the mucosa disappeared completely and the mucosal surface was, though somewhat eroded more or less recovered with a little less prominent infiltration of neutrophiles than before (i e. 24 hours later) In this period a beginning regeneration of epithelial cells is observed which are at first round in shape and of the basal cell type The epithelial layer increases day after day gradually in its thickness and on the 7th day it becomes 1 5 cells thick, while each cell is round or cylindrical in its shape but cilia are not yet found In this stage the infiltration of the neutrophiles is at its minimum (Fig 13a) and the obtained smears contain only the rounded epithelial cells (Fig 13b)

On the 14th day after instillation the cilia are already grown but only incompletely from the more or less plump cell body (Fig 14a)

On the 28th day the regeneration of the mucosal epithelium is perfect the ciliated cells are well formed the cilia and all other parts of the cell are completed (Fig 15a b)

In Fig 16 the above course is shown in a diagrammatic way The epithelial desquamation due to formol instillation becomes suddenly marked after instillation reaches a maximum in 3 hours, passes through a minimum in 24 hours and thereafter gradually increases while the wandering cells such as leucocytes etc delay more or less in appearance reach a maximum

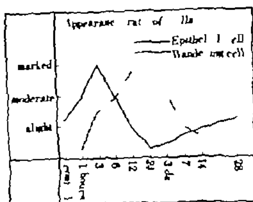


Fig. 16.

in 24 hours and then gradually decrease.

The correlations between the changes of the nasopharyngeal mucosa of r bbits with induced acute inflammation, especially the regenerating process of its epithelium and the cytological features in the smears are as gi en above. These correlations may suggest, in comparison with the nasopharyngeal smears of man, especially in the recovery stage during the treatment for nasopharyngitis, the true states of the inflammation called nasopharyngitis.

5) **Epithelial Changes during the Course of Local Treatment of Nasopharyngitis**

It is stated bove that the nasopharyngeal mucosal epithelium varies morphologically over a wide range and that its changes are related especially to the intensity of inflammation. In this paragraph the changes of epithelial features *during the local therapy of nasopharyngitis* will be referred to.

The treatment of nasopharyngitis consists generally in pplying l % zinc chloride solution (w th a little local anesthetic added) t the entire mucosal surface of the nasopharynx through the pharynx (w th pharyngeal w bs) and through the nose (w th nasal swabs) however severe pain is caused by *frequent* application and considerable hemorrhage *from* the mucosal surface is observed occasionally after pplication. In some cases the application may cause only a little pain and no hemorrhage and the cytological features *of smears in such* cases differ distinctly from those in cases w th severe pain or hemorrhage. I the former cases the epithelium is markedly desquamated and so transformed that it is swollen w th indistinct structure, *missing cuticular* borders, lacking cilia, etc. whereas in the latter cases the desquamated epithelial cells are scarce, normally elongated in their shape, and the cellular structure cilia, cuticular border etc. remain perfect

In the cases *w th nasopharyngeal h mor*rhages and severe pain at and after braslon desquamation and transformation of the epithelial cells is much more conspicuous. Moreover *in such cases w th marked epithelial desquamation and transformation numerous bacteria are* apt to appear associated w th an emigration of wandering cells such as neutrophile leucocytes, etc. however in the latter cases, i.e. those w thout noticeable pain due to abrasion, the bacterial organisms are so inconspicuous quantitati ely as w ll as qualitati ely that they are not easily found. There are scarcely any wandering bacteria to be found. From these findings it may be said that nasopharyngeal pain or hemorrhages due to mucosal abrasion suggest *the presence of inflammation in this part of the* body As stated bove, nasopharyngeal pain or hemorrhages at abrasion correspond w th the three outstanding cytological features in the smears obtained from the mucosa, i.e. epithelial desquamation, appearance of wandering cells and increase of bacterial organisms, so the correlations between these two components were studied n further detail.

Correlation between Abrasion Pain and the Degree of Exfoliation.

The mucosal abrasion of the inflamed nasopharynx with swabs causes severe pain and often *hemorrhages. This abrasion pain* was classed provisionally in 3 grades, i.e. marked~*moderate* (卌~卄) slight (+) and very slight~no pain (±~−) while the respective numbers of ciliated *epithelial cells exfoliated* n the smears in each microscopic field (×100) were class d as ery marked~numerous, passing *through* marked, moderate, slight and finally ery slight~less than 10, and the correlations *between both these* components were studied on both sides separately

As evidenced in T ble 11 in *cases with*

Table 11 Relation between abrasion pain and exfoliation degree of ciliated epithlial cells (320 sides)

exfoliation	abrasion pain		
	⧻~#	+	±~−
extrem marked	3	1	0
marked	40	21	8
moderate	28	47	25
slight	17	52	24
extrem. slight	2	25	27
total	90	146	84

abrasion pain ⧻~# + and ±~− the exfoliation degree is marked (40 cases) slight (52 cases) and very slight (27 cases) respectively It may be said therefore that the degree of nasopharyngeal abrasion pain varies almost in parallel with the exfoliation degree of ciliated epithelial cells.

Correlation between the Degree of Exfoliation and Transformation of Ciliated Epithelium

The frequency of appearance of the ciliated cells was graded as in the preceding paragraph and the cellular transformation was classed as 1) marked almost aciliated ill-defined poorly stained cells with markedly swollen cytoplasma and similar to Type-III in their shape passing through 2) moderate 3) slight and 4) normal type i e. in 4 grades Six cases were excluded in which most of the ciliated epithelial cells had not been exfoliated In cases with very slight exfoliation as given in Table 12 the transformation was slight~normal in 28 cases, i e it shows the high percentage of 69 % But in cases with slight moderate, and marked exfoliation, the transformation was mostly moderate and marked exfoliation the transformation was mostly moderate in 37 cases, i e 39 4 slight in 47 cases, i e 47 0 and slight in 35

Table 12 Relation between exfoliation degree of ciliated epithelial cells and their transformation degree (314 sides)

transformation	exfol.				
	extrem. marked	marked	moderat	slight	very slight
marked	0	6	14	17	9
moderate		25	32	37	10
slight	1	35	47	27	14
none	1	3	7	13	14
total	4	69	100	94	47

Table 13 Relation between transformation degree of ciliated epithelial cells and quantity of leukocytes (314 sides)

leukocytes	deform.		
	marked	moderate	slight normal
⧻	11	12	
#	15	25	26
+	10	49	68
normal	9	19	68
total	45	105	164

cases i e. 50 7% respectively So there is no definite correlation between the two components except in cases with very slight exfoliation Contrary to the fact of the parallel course of abrasion pain with that of exfoliation, the transformation of the epithelial cell does not necessarily go parallel with its exfoliation.

Correlation between the Degree of Exfoliation of Ciliated Epithelium and the Leucocytes Appearing in the Smears

The appearance of leucocytes and lymphocytes was classed as marked (⧻) numerous, having an even distribution in the smears, passing through moderate (#) slight (+) and normal as shown in Table 13 In the cases with marked moderate and slight~normal transformation the appearance of leucocytes was mostly #~⧻ in 26 (26/45 = 57 8 %) +~# in 74 (74/105 = 70 5 %) and normal −~+ in 136 cases (136/164 = 82 9) respectively In other words leucocytes appeared in the overwhelming majority of cases. In cases with marked moderate and slight transformation the appearance of leucocytes was mostly # in 15 + in 49 and + or normal in 68 cases therefore the transformation of the epithelial cells appears more or less to parallel the appearance of leucocytes In short the exfoliation of the epithelial cells due to nasopharyngeal abrasion runs relatively parallel to the local pain at abrasion and also somewhat parallel to the regional appearance of leucocytes whereas the degree of exfoliation and that of the transformation of exfoliated cells do not particularly parallel each other Clinical experience indicates that the abrasion of the regional mucosa of the nasopharynx with acute or subacute inflammation causes pain proportional to the in

tensity of inflammation, and furthermore hemorrhages are frequently found after abrasion. This will be elucidated by observation of the inflammation in its recovery process under local treatment.

Microscopic observation of the smears obtained from the nasopharyngeal mucosa with severe abrasion pain reveals, therefore, desquamation of epithelial cells, proliferation of bacteria and emigration of leucocytes, which are increased with the severity of abrasion pain. The cytological findings of the smears, such as epithelial desquamation, bacterial flora and leucocytic emigration improve as the abrasion pain or hemorrhages gradually decrease during local treatment for nasopharyngitis, and finally are normalized with disappearance of abrasion pain and hemorrhages, namely the epithelial desquamation diminishes and the bacteria as well as leucocytes disappear. The above mentioned studies go into further details of such clinical findings and reveal that the epithelial desquamation found in the smears runs parallel to the local abrasion pain. Incidentally the abrasion pain of the nasopharynx increases, as mentioned previously, almost in direct proportion to the intensity of inflammation and changes generally in parallel to cytological features of the smears. However marked epithelial desquamation and appearance of bacteria as well as wandering cells are to be found in some cases without noticeable abrasion pain. In such cases the desquamated epithelial cells are often transformed and associated also with the appearance of leucocytes, goblet cells, etc. Clinically the patients complain of a posterior rhinorrhea (despite absence of sinusitis) and the disease is often refractory to local treatment. Nasopharyngitis of this type is designated chronic nasopharyngitis by the author, whereas that with severe abrasion pain is referred to as subacute nasopharyngitis.

Acute nasopharyngitis corresponds to an acute stage of subacute nasopharyngitis with repeated relapse and especially with visible symptoms, i.e., a feeling of dryness on the dorsal surface of the soft palate and a slightly open nasal voice, the so-called "grippe voice". This acute nasopharyngitis is the so-called cold and the symptoms appearing in case of a cold, such as headache, fever, general feebleness, etc. can be connected with subacute nasopharyngitis, as will be mentioned in the following. When treatment is given for acute nasopharyngitis from this viewpoint, a cold is observed to disappear very soon thereafter.

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The appearance of leucocytes and lymphocytes was classed as marked (╫) numerous, having an even distribution in the smears, passing through moderate (╫) slight (+) and normal as shown in Table 13 In the cases with marked moderate and slight~normal transformation the appearance of leucocytes was mostly ╫~╫ in 26 (26/45 = 57 8) +~╫ in 74 (74/105 = 70.5) and normal −~+ in 136 cases (136/164 = 82 9) respectively In other words leucocytes appeared in the overwhelming majority of cases. In cases with marked moderate and slight transformation the appearance of leucocytes was mostly ╫ in 15, + in 49 and + or normal in 68 cases therefore the transformation of the epithelial cells appears more or less to parallel the appearance of leucocytes. In short the exfoliation of the epithelial cells due to nasopharyngeal abrasion runs relatively parallel to the local pain at abrasion and also somewhat parallel to the regional appearance of leucocytes, whereas the degree of exfoliation and that of the transformation of exfoliated cells do not particularly parallel each other Clinical experience indicates that the abrasion of the regional mucosa of the nasopharynx with acute or subacute inflammation causes pain proportional to the in

tensity of inflammation, and furthermore hemorrhages are frequently found after abrasion. This will be elucidated by observation of the inflammation in its recovery process under local treatment.

Microscopic observation of the smears obtained from the nasopharyngeal mucosa with severe abrasion pain reveals, therefore, desquamation of epithelial cells, proliferation of bacteria and emigration of leucocytes, which are increased with the severity of abrasion pain. The cytological findings of the smears, such as epithelial desquamation, bacterial flora and leucocytic emigration improve as the abrasion pain or hemorrhages gradually decrease during local treatment for nasopharyngitis, and finally are normalized with the disappearance of abrasion pain and hemorrhages, namely the epithelial desquamation diminishes and the bacteria as well as leucocytes disappear. The above mentioned studies go into further details of such clinical findings and reveal that the epithelial desquamation found in the smears runs parallel to the local abrasion pain. Incidentally, the abrasion pain of the nasopharynx increases, as mentioned previously, almost in direct proportion to the intensity of inflammation and changes generally in parallel to cytological features of the smears. however, marked epithelial desquamation and appearance of bacteria as well as wandering cells are to be found in some cases without noticeable abrasion pain. In such cases the desquamated epithelial cells are often transformed and associated also with the appearance of leucocytes, goblet cells, etc. Clinically the patients complain of a posterior rhinorrhea (despite absence of sinusitis) and the disease is often refractory to local treatment. Nasopharyngitis of this type is designated chronic nasopharyngitis by the author, whereas that with severe abrasion pain is referred to as subacute nasopharyngitis.

Acute nasopharyngitis corresponds to an acute stage of subacute nasopharyngitis with repeated relapse and especially with notable symptoms, i.e. a feeling of dryness on the dorsal surface of the soft palate and a slightly open nasal voice, the so-called "grippe-voice". This acute nasopharyngitis is the so-called cold and the symptoms appearing in case of a cold, such as headache, fever, general feebleness, etc. can be connected with subacute nasopharyngitis, as will be mentioned in the following. When treatment is given for acute nasopharyngitis from this viewpoint, a cold is observed to disappear very soon thereafter.

6 Pathogenesis of Nasopharyngitis

Nasopharyngitis occurs at first as a reactive inflammation with physical and chemical actions caused by atmospheric dust particles attached to the nasopharyngeal wall which were drawn in with the air through the nasal cavities Such an incipient inflammation is naturally of such a slight degree, that it is probably invisible and is essentially a reversible process unless the stimuli are repeated Al though this inflammation will disappear if the causal stimuli are removed still this reversibility of the inflammation is unlikely for the following reasons

1) The air cannot be absolutely clear and the nasopharyngeal irritation by dust particles occurs without interruption

2) This irritation is due not only to the physical action of dust particles, but also to the chemical stimuli of their soluble elements or gaseous substances, e g sulfur dioxide.

3) Once an inflammation is initiaed by primary irritation the subsequent stimuli cause a much more intense reaction than the previous time

4) The bacteria on the dust particles attach to the nasopharyngeal wall and if inflammation exists and the bacteria are well adapted to the environment proliferate further and the proliferation itself makes the inflammation worse

5) Some of the bacterial flora after they have once contaminated and connected them selves with an inflammation preserve always their minimum life wheather they repeat more or less alteration according to that of environ ment They survive further as weeds grow and may play a significant role in aggravation of th inflammation while they recover them selves under favourable circumstances. The bacteria causing chronic inflammations in these ways are staphylococcus aureus, pseudomonas aeruginosa and proteus the so-called Gram negative bacilli

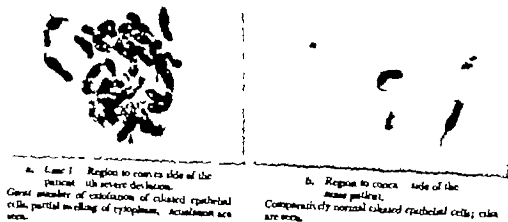
6) In the case of acute exacerbation of the inflammation the above mentioned bacteria increase markedly hemolytic streptococci, pneumococci etc. make their appearance again, and pseudomonas aeruginosa is occasionally found. These bacterial organisms disappear or become markedly weak, when the acute stage of the inflammation has passed

7) Inflammatory foci in the nasopharynx, once developed and fixed, chagne according to the general conditions. In cases for instance, of a cold the nasopharyngitis recurs acutely The author is of the opinion that the oppor tunity for this recurrence should be regarded as a sort of conditioned reflex resulting from inflammatory foci with acute exacerbation which has become chronic due to certain alterations in physical conditions.

8) The word conditioned reflex may sound strange but in understanding the process of inflammation it is convenient to imagine a reflex process e g a reflex under certain con ditions via the autonomic nervous system and resulting for instance in salivation. For this purpose experimental studies are of course required but they have not been made at present By observation of the nasopharynx in case of a cold the presence of an extensive acute inflammation in the nasopharynx is always ascertained Nasopharyngitis in its latent stage of inflammation has very significant effects on the autonomic nervous system of the whole body and the autonomic nerves in the case of a marked inflammation become, as our experi ments indicated hypersensitive and such a hypersensitivity is, as is also demonstrated restored to normal by treatment of the naso-pharynx. Since the nasopharyngitis associated with a cold, however always develops severe (mostly local) symptoms, the general symptoms of a cold are to be regarded as referable to acute nasopharyngitis. In the case of a cold caused as mentioned previously by chilling as a dyna mic stimulus (e.g abrupt fall of temperature

etc.) these dynamic changes of temperature lead to an acute inflammation (relapse) of the nasopharynx. This means a relation between nasopharyngitis and changes in temperature and le da us to advance the hypothesis that changes in temperature cause an acute exacerbation of persistent nasopharyngitis. The correlations between these two components appeared to be a phenomenon like a conditioned reflex. That is, certain chronic inflammatory foci may for instance, progress into the acute stage under a certain physical condition. One of the experiments designed by me consists in leading the chronic inflammation, if possible, into an acute stage by chilling young animals with induced chronic inflammatory foci which are conditioned to become acute with simultaneous partial chilling of the body and corresponding stimulation of the inflammatory foci.

9) Differences of ventilation with regard to the laterality of the nasal cavity also controls over the inflammations of the nasopharynx. According to the experiments in cases of septum deviation conducted by Inx (1963b) of our clinic, differences of inflammation can be observed between the nasopharyngeal walls on the deviated and the opposite side. In cases of septum deviation showing distinct differences of ventilation with regard to the laterality it was, therefore, elucidated that the inflammation of the nasopharyngeal wall adjacent to each choana, e.g. of the dorsal surface of the soft palate differs significantly in its intensity with regard to the laterality. A comparative examination of the smears prepared separately from the mucosa of the dorsal surface of the soft palate adjacent to the choanae with nasal swabs introduced through bilateral nasal cavities separately into the nasopharynx reveals that the inflammation of the mucosa shows a higher degree of activity on the deviated side than on the opposite side (Figs. 17–19). The more obvious the septum deviation, the more significant this difference of activity becomes. According to the model experiment made by Inx it has become clear that the adhesion of dust particles to the nasopharyngeal wall is especially marked on the deviated side in the case of remarkable septum deviation. In Table 14, 15 and 16 are given the differences of (subjective) nasal obstruction on the deviated side, the more severe is the inflammation of the nasal mucosa on the occluded side. This tendency is to be found also in cases of moderate deviation, although not so marked as in cases of marked deviation. The difference of the degree of nasopharyngitis with regard to the laterality is less significant in cases of slight septum deviation. The differences of ventilation through the nasal cavities with regard to the laterality parallel to those of inflammation of the dorsal surface of the soft palate adjacent to each choana and the nasopharyngeal inflammation is, as mentioned previously, more severe on the



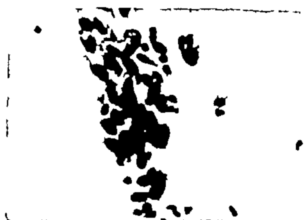
a. Case 1. Region to convex side of the patient with severe deviation.
Great number of exfoliation of ciliated epithelial cells, partial swelling of cytoplasm. Ciliolysis are seen.

b. Region to concave side of the same patient.
Comparatively normal ciliated epithelial cells; cilia are seen.

Fig. 17 Epithelial smeargrams of nasopharyngeal mucosa to convex and concave side of nasal septum.



a. Case 3 Region to convex side of the patient with severe deviation
Swelling of the cytoplasm in many of the epithelial cells, deformation and poor staining are remarkable Little cilia and striated borders are perceived. Leukocytes and lymphocytes are mingled.

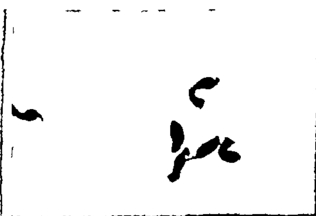


b. Region to concave side of the same patient.
Small number of goblet cells are mingled with ciliated epithelial cells Type III A part of the epithelial cells is swollen and vacuolated together with the disappearance of cillia and striated borders.

Fig 18.



a. Case 5 Region to convex side of the patient with less severe deviation
Many ciliated epithelial cells are exfoliated Deformation is not so remarkable Striated borders and cilia are seen.



b. Region to concave side of the same patient.
Ciliated epithelial cells with almost normal cilia.

Fig 19

Table 14 Comparison of nasal obstruction between convex and concave side of nasal septum

obstruct.	deviation								
	severe (44 cases)			less severe (38 cases)			mild (58cases)		
	convex								
concave	#~#	+	±~−	#~#	+	±~−	#~#	+	±~−
#~#	0	0	0	1	1	0	2	0	1
+	16	5	0	13	8	1	6	16	0
±~−	10	7	6	6	14	14	1	7	25
total	26	12	6	20	23	15	9	23	26

Table 15 Comparison of abrasion pain in nasopharynx between convex and concave side in cases of nasal septum deviation

abrasion pain	deviation											
	severe (44 cases)				less severe (38 cases)				mild (38 cases)			
convex	concave											
	#~#	+	±	−	#~#	+	±	−	#~#	+	±	−
#~#	1	0	0	0	3	2	0	0	1	7	1	1
+	19	8	0	0	21	10	2	0	13	8	2	0
±	6	6	1	1	4	2	3	0	1	5	8	0
−	0	1	1	1	1	4	0	3	2	5	0	2
total	26	13	2	1	29	18	8	3	19	23	11	3

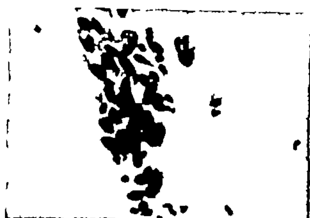
Table 16 Comparison of exfoliation degree of ciliated epithelial cells in nasopharynx between convex and concave side in cases of nasal septum deviation

exfol.	deviation														
	severe (44 cases)					less severe (38 cases)					mild (38 cases)				
	convex														
concave	extrem. marked	marked	moderate	slight	extrem. slight	extrem. marked	marked	moderate	slight	extrem. slight	extrem. marked	marked	moderate	slight	extrem. slight
extrem. marked	0	0	1	0	0	0	2	0	0	0	0	1	0	0	0
marked	0	1	0	0	0	0	1	3	1	1	0	1	2	2	1
moderate	0	7	2	0	1	1	8	4	2	1	0	8	8	6	0
slight	1	9		1	0	0	5	7	7	3	0	3	2	9	1
extrem. slight	0	7	7	2	0	0	1	7	4	0	0	1	3	9	1
total	1	24	15	3	1	1	17	21	14	5	0	14	15	26	3

deviated, i.e. narrowed side. The reason is that the inflammation was further intensified by dust collecting in a part of the nasopharynx adjacent to the choana like a drift, where the air inhaled separately through bilateral nostrils flow with less energy on the side with less ventilation than the opposit side. The marked inflammation caused in this way also causes an aggravation of the inflammatory changes in the adjacent tissue, and constitutes a factor contributing toward aggravation of the inflammation of the entire nasopharynx. This is the reason why so-called intranasal orthopedic treatment symmetrizing bilateral ventilation is regarded as an important element in cases of nasopharyngitis. Although the intranasal-orthopedists have hitherto stated very abstractedly functional improvement of the body by regulating the air passages " yet it can readily be explained by introducing such a concept in their viewpoint, as the localization of nasopharyngitis owing to the difference of ventilation with regard to the laterality because of the septum deviation, etc. as mentioned above. In other words, irregularity of the intranasal air flow—nasopharyngitis—various kinds of general disease resulting from nasopharyngitis.



a. Case 3: Region to convex side of the patient with severe deviation.
Swelling of the cytoplasm in many of the epithelial cells, deformation and poor staining are remarkable. Little cilia and striated borders are perceived. Leukocytes and lymphocytes are mingled.

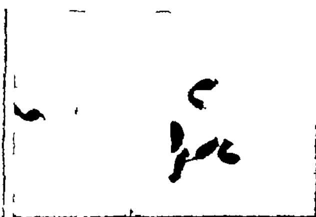


b. Region to concave side of the same patient.
Small number of goblet cells are mingled with ciliated epithelial cells Type III. A part of the epithelial cells is swollen and vacuolated together with the disappearance of cillia and striated borders.

Fig 18.



a. Case 5. Region to convex side of the patient with less severe deviation.
Many ciliated epithelial cells are exfoliated. Deformation is not so remarkable. Striated borders and cilia are seen.



b. Region to concave side of the same patient.
Ciliated epithelial cells with almost normal cilia.

Fig 19

Table 14 Comparison of nasal obstruction between convex and concave side of nasal septum

obstruct. concave	deviation: severe (44 cases) convex #∼#	+	+∼−	less severe (58 cases) convex #∼#	+	±∼−	mild (58 cases) convex #∼#	+	+∼−
#∼#	0	0	0	1	1	0	2	0	1
+	16	5	0	13	8	1	6	16	0
±∼	10	7	6	6	14	14	1	7	25
total	26	12	6	?0	23	15	9	23	?6

strate the presence of erosion on the mucosal surface.

The pain during and after abrasion of the nasopharyngeal mucosa with local hemorrhages establishes proof of the presence of inflammations, especially of acute or subacute ones. This fact will be confirmed by clinical course of the ailment and by the transition of smears from mucosal abrasion specimens observed successively during the course. The previously mentioned abrasion pain or postbrasiv hemorrhages, as stated already parallel the severity of inflammation found in the smears. When hemorrhages or pain during treatment is gradually reduced only by nasopharyngeal local treatment (daily application of 1% $ZnCl_2$) the cytological findings of the smears will be, in accordance with the treatment, gradually improved and finally in the smears from the nasopharyngeal mucosa will be lacking entirely in abrasion pain and hemorrhages, desquamated epithelial cells will be scarce, wandering cells will disappear completely and bacterial content will also be decreased markedly.

In regard to the nasopharynx, in short, inflammations are originally present, so its normal aspect does not appear till these inflammations are cured. Cases in which almost normal smears can be obtained unless treated from beginning are seldom, if ever to be found. According to our investigation moderate inflammation was found in 69.8% of 202 schoolchildren examined and marked nasopharyngitis was, as will be mentioned later found in about 80% of 4 000 out-patients.

The findings in cases with severe inflammation are given in the following in comparison with those in almost healed cases.

	Nasopharyngitis	
Findings	marked	slight
Epithelium	Desquamation & Deformation, marked	Normal Epithelial Cells
Wandering Cells	present	(−)
Bacterial Content	increased in number and kind	very low
Abrasion Pain	(#)	(±)∼(−)
Postabrasion Hemorrhage	(#)∼(+)	(−)

The local diagnosis of nasopharyngitis is, in consideration of these results, to be made as follows

1 Abrasion pain in the nasopharyngeal mucosa caused by swabs.

2 Hemorrhages during abrasion of the nasopharyngeal mucosa caused by swabs (only in cases of marked inflammation with erosion)

3 Smears of nasopharyngeal abrasion specimens (smears prepared with abrasion swabs)

i. Desquamated epithelium Papanicolaou Staining
ii. Wandering cells Giemsa Staining
iii. Bacteria Culture identification, oil immersion

Furthermore, the posterior rhinoscopic and nasopharyngoscopic findings are also to be referred to. Nasopharyngitis exists always or almost always regardless of the presence or absence of inflammations of adjacent organs, so that even the absence of inflammations of adjacent organs, e.g. of tonsillitis or pharyngitis, does not afford conclusive evidence against the presence of nasopharyngitis.

7 Diagnosis of Nasopharyngitis

Concerning the disease called nasopharyngitis, little has been discussed up to this time in medical science The existence of such an inflammation is however quite possible and can actually be demonstrated in a great many subjects. Nevertheless this has not been made the subject of medical studies for many reasons such as the following

1 Nasopharyngitis is mostly latent without local symptoms and there are rarely subjective complaints.

2 The nasopharynx is a structure which light can hardly reach. Accordingly the presence of slight nasopharyngeal lesions such as simple inflammation cannot always be determined by conventional optical methods.

As a local sign of nasopharyngitis in its acute onset there can be found a feeling of dryness in the base of nasopharynx i e. on the dorsal surface of the soft palate. This sign corresponds with an abnormal feeling in the soft palate mostly encountered in early stages of a cold and with an open nasal voice called grippe vioce (a kind of nasal voice, entirely different from the closed nasal voice which is due to nasal obstruction owing to a cold accompanied by rhinitis) This feeling of abnormality of dryness appearing on the dorsal surface of the soft palat often spreads, however into the throat or pharyngolaryngological region. In many cases it is complained of as an abnormal feeling in the throat region and it is natural that the physician is apt to investigate only the findings of the mesopharynx or larynx and diagnoses as pharyngitis laryngitis or sometimes as a nervous complaint showing no change in the throat In such cases, however the origin of the bad feeling in throat can easily and clearly be discovered by swabbing the nasopharynx

The existence of pharyngitis or laryngitis must not be neglected The diagnosis of these diseases can be carried out as follows local hyperemia and pain when swallowing (especially on one side of pharynx) in pharyngitis, hoarseness and vocal cord hyperemia in laryngitis) But even in these cases the complication of nasopharyngitis is always present and the direct treatment of this nasopharyngitis will make the progress of the original inflammation better

Furthermore this abnormal feeling in the soft palate or the open nasal voice appears for the most part exclusively in the early stages of a cold and disappears within 1–2 days. Still a severe inflammation persists in the nasopharynx. Although such inflammation should naturally be understood by the redness of the mucosa, etc. its perfect diagnosis is seldom if ever possible because the light can hardly reach this part of the body and the nasopharyngeal mucosa is primarily red in color The presence of this inflammation cannot be observed sufficiently and exactly by simple optical methods. Therefore the method must depend for accuracy on the diagnostic method described by the author as follows.

The Method of Diagnosis of Nasopharyngitis

The diagnostic method for nasopharyngitis developed by the author is as follows as a diagnostic procedure the abrasion of the regional mucosa is exclusively applied without depending upon optical methods. In cases with severe inflammation the abrasion of nasopharyngeal mucosa especially of the dorsal surface of the soft palate by (nasal and pharyngeal) swabs is accompanied by severe pain followed frequently by postabrasive mucosal hemorrhages. The abrasion pain may often persist after abrasion and if intense even for several hours. In cases with severe hemorrhages the blood flows down through nasal cavities or pharynx and the hemorrhages often continue though only in small quantities, even for several hours. Such hemorrhages due to abrasion of the nasopharyngeal mucosa demon

strate the presence of erosion on the mucosal surface.

The pain during and after abrasion of the nasopharyngeal mucosa with local hemorrhages establishes proof of the presence of inflammations, especially of acute or subacute ones. This fact will be confirmed by clinical course of the ailment and by the transition of smears from mucosal abrasion specimens observed successively during the course. The previously mentioned abrasion pain or post abrasive hemorrhages, as stated already parallel the severity of inflammation found in the smears. When hemorrhages or pain during treatment is gradually reduced only by nasopharyngeal local treatment (daily application of 1% $ZnCl_2$) the cytological findings of the smears will be, in accordance with the treatment, gradually improved and finally in the smears from the nasopharyngeal mucosa will be lacking entirely in abrasion pain and hemorrhages, desquamated epithelial cells will be scarce, wandering cells will disappear completely and bacterial content will also be decreased markedly

In regard to the nasopharynx, in short, inflammations are originally present, so its normal aspect does not appear till these inflammations are cured. Cases in which almost normal smears can be obtained unless treated from beginning are seldom, if ever to be found. According to our investigation moderate inflammation was found in 69.8 of 202 schoolchildren examined and marked nasopharyngitis was, as will be mentioned later found in about 80% of 4 000 out-patients.

The findings in cases with severe inflammation are given in the following in comparison with those in almost healed cases.

Findings	Nasopharyngitis marked	slight
Epithelium	Desquamation & Deformation, marked	Normal Epithelial Cells
Wandering Cells	present	(−)
Bacterial Content	increased in number and kind	very low
Abrasion Pain	(+)	(±)~(−)
Postabrasiv Hemorrhage	(+)~(+)	(−)

The local diagnosis of nasopharyngitis is, in consideration of these results, to be made as follows:

1 Abrasion pain in the nasopharyngeal mucosa caused by swabs.

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3 Smears of nasopharyngeal abrasion specimens (smears prepared with abrasion swabs)

- i. Desquamated epithelium Papanicolaou Staining
- ii. Wandering cells Giemsa Staining
- iii. Bacteria Culture, identification, oil immersion

Furthermore, the posterior rhinoscopic and nasopharyngoscopic findings are also to be referred to. Nasopharyngitis exists always or almost always regardless of the presence or absence of inflammations of *adjacent* organs, so that even the absence of inflammations of adjacent organs, e.g. of tonsillitis or pharyngitis, *does not afford conclusive evidence against the* presence of nasopharyngitis.

8 Observations of the Course of Nasopharyngitis (Especially with Alterasion of Abrasion Pain)

In the preceding chapter it was stated that the diagnosis of nasopharyngitis cannot be made definitely by any of the hitherto known oto-rhinolaryngological methods, but only by cytological examination of smears obtained from nasopharyngeal mucosa and by observation of abrasion reactions such as pain or hemorrhages and that the abrasion of nasopharyngeal wall (dorsal surface of the soft palate) can be done without any difficulty and specimens can be obtained without causing any damage to the local tissue, as long as the inflammation is not severe (in cases of severe inflammation with mucosal erosion—probably due to formation of minute granulation tissue— the abrasion with swabs easily causes mucosal damages, but this management itself constitutes local treatment) This method is, therefore to be applied even everyday and only swabs for local treatment of nasopharyngitis dipped in 1 $ZnCl_2$ (or any other corrosive agent) and applied (always carefully and sufficiently) to the nasopharyngeal mucosa can obtain abrasion specimens for smears which are to be observed successively (even daily without trouble) so that the nasopharyngitis can be observed in this entire course.

Our object of observation in cases of nasopharyngitis was to examine three smears obtained as above at the time of daily treatment and stained each for desquamated epithelial cells wandering cells and bacteria The treatment consists as stated already of the application of 1 $ZnCl_2$ (eventually with small quantities of xylocain added) with swabs to nasopharyngeal mucosa so we have thoroughly studied for the first time the effects of drugs added to each of the specimens. No essential differences in the effect of abrasion by swabs with and without drugs were noted at least as far as determined on smears. In collecting bacteria for culture, for instance, sterilized swabs should be used and care must be taken not to bring the swabs at the time of collection into contact with the mucosa of oral cavity mesopharynx or nasal cavities. Of course nasopharyngitis, judging from the findings of such smears however is profoundly influenced by the presence of pain hemorrhages, etc. at the time of abrasion The fact that the pain of abrasion of the nasopharyngeal mucosa parallels the intensity of the inflammation, applies not only to the nasal mucosa but also to the meso- and hypopharynx, the inner surface of the esophagus, etc.

Great importance has been attached as you know to calor dolor tumor and rubor as classical criteria for inflammation, of which the three criteria other than rubor are mostly disregarded as far as mucosal inflammation is concerned. Of course this definition is not necessarily to be applied directly to mucosal inflammation. From the correlation of the findings of smears and abrasion pain with, however it should be considered that the dolor caused by abrasion may play the most significant role at least in the development of nasopharyngeal inflammation.

The dolor which has been considered to be of little significance in mucosal inflammation, however should play a more significant role as far as the nasopharynx (where the redness cannot be as satisfactorily observed as the other parts of the mucosal tissue) is concerned and its importance must be taken into consideration in observing the clinical course

Abrasion Pain and Nasopharyngitis

As stated above clinical observation of abrasion pain (as well as hemorrhages at the time of abrasion) in parallel to smears or if necessary the observation of nasopharyngitis in its entire course in terms of abrasion pain rather than smears, makes it possible to distinguish inflammatory conditions. The results are as follows

1 Acute Nasopharyngitis

In this case the abrasion pain is most marked and w th frequent hemorrhages, and not rarely as stated already local abnormal feeling appears (In most cases the so-called feeling of a cold is observed) This is due to a stimulation of the autonomic nerves by acute nasopharyn gitis, so the treatment of the nasopharynx readily cures colds and makes possible the prevention of colds as well. The soft palate will often be slightly paralyzed and in con sequence the voice becomes slightly hoarse from a cold. This is an open nasal voice characteristic in m, n, ŋ etc., unlike the closed nasal voice of acut rhinitis due to a cold. Such acute nasopharyngitis should properly however be referred to as an acute exacerbation of nasopharyngitis When nasopharyngitis manifests itself, the symptoms of a cold, as mentioned earlier such as fever etc. may become evident. Daily observation of the course of nasopharyngitis with nasopharyngeal abrasion specimens reveals, however that an acute exacerbation can also be encountered in the stat even w tho t manifestation of cold and differs widely in ts grade too

After an established acute exacerbation, however the abrasion pain of nasopharyngeal mucosa more or less increases. Nasopharyn gitis exists latently in a large number of people troubled w th recurrent acute exacerbation however the reason for this fact raises difficult problems. The uthor' own opinion has already been given.

2 Subacute Nasopharyngitis

This is the most common and, therefore, the most frequent type of nasopharyngitis. Strictly speaking, we cannot, however draw a fine between acute and subacute nasopharyngitis. Subacut nasopharyngitis may therefore, represent only average nasopharyngitis. By subacute nasopharyngitis we mean the type of nasopharyngitis other than the previously mentioned acute nasopharyngitis or the chronic nasopharyngitis. Its characteristics are as follow

Local brasion pain occurs during and after abrasion of nasopharynx.

ii. Desquamation of the epithelium is marked in the smears.

iii. Bacteriological examination reveals the so-called chronic phlogistic bacteria, such as pathogenic staphylococci, gram-negative bacilli, etc.

iv. No local symptoms are complained of except at the time of abrasion.

v. Erosion is common in acute cases however it also occurs in subacute and especially n infantile cases.

vi. The disease responds often and readily to local treatment.

3 Chronic Nasopharyngitis

By "chronic nasopharyngitis" we mean a process that occurs, but not very frequently Briefly its symptoms are as follows

(Purulent) rhinorrhea.

ii. Abundant neutrophil leucocytes in the smears w th marked desquamation and degeneration of epithelial cells.

iii. Abrasion pain and bleeding not very marked.

iv Relatively long course despite treatment, etc.

The abrasion pain is more or less marked, except in chronic cases, and the more marked the pain is, the more evident the symptoms may become. In acute and subacute cases, however the inflammation can generally be improved rapidly by local treatment, but in some cases the local treatment is not alw ys effective and the abrasion pain remains for a long period of time. In such cases only a slight effect of the nasopharyngeal therapy on general diseases is to be expected.

The local therapeutic effect on abrasion pain and postabrasive hemorrhages was observed by SAITO (1963) in 30 cases of nasopharyngitis in our clinic. 1 $ZnCl_2$ solution was applied daily to the nasopharyngeal mucosa (especially of the dorsal surface of the soft palate) and then

Table 17 Days until disappearance of abrasion pain and abrasion hemorrhage during success treatment of nasopharyngitis.

days		2 5	10	15	20	30	total
abrasion pain	cases	3	10	13	1	3	30
	%	10	33.3	43.3	3.3	10	100
hemor rhage	cases	8	9	5	1	2	25
	%	32	36	20	4	8	100

Table 18 Exfoliation of epithelial cells before and after treatment.

exfoliation of epithelial cells	before	after	cases	total
decreased	++++	++	2	25
	+++	+	12	
	++	+	11	
unchanged	++	++	1	5
	+	+	4	

pain and hemorrhages after application were observed in detail The results were as given in Table 17 namely despite probable long standing inflammation before therapy the abrasion pain and postabrasive hemorrhages disappeared at the latest within 1 month after therapy and in the great majority of cases, within 15 days. The desquamation of the epithelial cells was improved, as shown in Table 18 running parallel to clinical manifestations such as abrasion pain etc.

In 1/5 of the cases little improvement was observed for instance in desquamation of epithelial cells, despite treatment. Such cases probably pertain to the so-called chronic nasopharyngitis, and the cases with abrasion pain or postabrasive hemorrhages which are favorably influenced by treatment are defined as subacute (as well as acute) nasopharyngitis.

9 Epidemiology of Nasopharyngitis

As mentioned in the first chapter nasopharyngitis exists latently in a large number of people, and pathological examination revealed the presence of inflammation in all subjects aged from 12 hours after birth to 80 years. By the bacteriological examination of nasopharynx of infants, as shown in Table 5 staphylococcus epiderm. is found in 4 out of 14 cases even on the first day after birth, and thereafter the various kinds of bacteria increased gradually. Only a few cases remained sterile beyond the fourth day. Although the contamination with bacteria does not necessarily cause inflammation immediately in the majority of cases, such the one of nasopharyngeal inflammation 12 hours after birth, it is supposed that the infection can be caused very early by atmospheric dust particles and the bacteria attached thereto.

In Table 19 the results of nasopharyngeal examination are given, which were performed on 202 primary school children in the city of Tokyo, especially in districts with a contaminated atmosphere. Their inflammatory states were studied by smears. This examination revealed that nasopharyngitis was marked in 83 cases (42.1%) and moderate in 56 cases (27.7%), so it was evident in a total of 69.8%, but without subjective symptoms in the majority of cases. In other words nasopharyngitis was present in about 70% of the school children.

The examination of 4,616 patients visiting our ENT-Clinic revealed, as shown in Table 20,

Table 19 Frequency of nasopharyngitis in school children (1964, 12)

Age	normal to slight	moderate	marked	total
6	6	11	14	31
7	10	7	22	39
8	18	6	35	59
9	8	7	21	36
10	11	9	11	31
11	8	14	8	30
total	61 (30.2%)	56 (27.7%)	85 (42.1%)	202

Table 20 Frequency of nasopharyngitis in patients visited our clinic.

	number of examined cases	chronic	acute
male	2,553	1,727 (67.6%)	390 (15.4%)
female	2,063	1,390 (67.3%)	342 (16.6%)
total	4,616	3,117 (67.4%)	732 (15.9%)

Table 21 Frequency of nasopharyngitis with regard to age group.

age	number of examined cases	subacute or chronic	acute
0–9	662	308 (46.5%)	178 (26.9%)
10–19	708	490 (69.1%)	118 (16.7%)
20–29	1,228	869 (70.7%)	185 (15.1%)
30–39	785	578 (73.6%)	111 (14.1%)
40–49	545	399 (73.1%)	57 (10.5%)
50–59	387	278 (71.2%)	47 (12.2%)
60–	301	195 (65.0%)	36 (11.9%)

that subacute or chronic nasopharyngitis was present in 67.4% and these cases are, as an interesting fact, quite similar to those of the school children. A so-called cold was found in 15.9% of the cases.

The incidence of nasopharyngitis is, therefore, altogether more than 80%. From the fact that an acute exacerbation of nasopharyngitis occurs in case of a cold and in consideration of the morbidity of a cold in the majority of cases, it is no wonder that such a high incidence of latent inflammation can be found.

In Table 21 the same cases were shown in respect to each age group. From this table it can be seen that the incidence-ratio between subacute or chronic and acute inflammation differs widely with different age groups, i.e. less than and more than 9 years of age. Namely in cases of less than 9 years of age the acute inflammation is common, whereas the subacute one is rather rare. From the clinical point of view severe inflammation such as erosion in its acute exacerbation should actually be found in

Table 18 Exfoliation of epithelial cells before and after treatment.

exfoliation of epithelial cells	before	after	cases	total
decreased	+++	++	2	25
	+++	+	12	
	++	+	11	
unchanged	++	++	1	5
	+	+	4	

pain and hemorrhages after application were observed in detail The results were as given in Table 17 namely despite probable long standing inflammation before therapy the abrasion pain and postabrasive hemorrhages disappeared at the latest within 1 month after therapy and in the great majority of cases, within 15 days. The desquamation of the epithelial cells was improved, as shown in Table 18, running parallel to clinical manifestations such as abrasion pain etc.

In 1/5 of the cases little improvement was observed for instance in desquamation of epithelial cells despite treatment Such cases probably pertain to the so-called chronic nasopharyngitis, and the cases with abrasion pain or postabrasive hemorrhages which are favorably influenced by treatment are defined as subacute (as well as acute) nasopharyngitis.

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10 Significance of Nasopharyngitis for the Whole Body

Examination of nasopharyngitis by our methods reveals that remarkable inflammatory findings persist also in the nasopharyngeal mucosa already free from local symptoms after a cold, and further in cases without an existing cold nasopharyngeal examination also shows latent inflammation frequently. The majority of the hosts (carriers of inflammation) are not conscious of the existing inflammation of the nasopharynx at all. Therefore, in most cases the nasopharyngitis proceeds without being noticed.

This fact is one of the most important characteristics of nasopharyngitis. In the presence of certain disease, especially inflammation, there should usually be some abnormalities in the region, of which the patient complains and sees physician for.

The local symptoms suggest the beginning of the disease, for instance, otorrhea, otalgia, defective hearing etc. in otitis media and anal hemorrhages or pain in hemorrhoids, therefore, the complete disappearance of such symptoms should be identical with recovery. The early detection of the diseases, for instance of malignant tumors before symptomatic manifestation has been attempted due to the gradual progress in medical science, which facilitated great progress in the field of medicine.

At present, however the chief complaints of external manifestations are only criteria of the disease at least as far as inflammation is concerned. This means probably that little progress has been made in the conventional view which regards inflammation, unlike malignant tumors, as a less important disease necessitating little or no early detection. It might reasonably be expected that progress in the field of today medicine be made along this line of study.

Nasopharyngitis is a disease left behind as a subject of medical investigation up to this time. If the nasopharynx has only a local inflammation, there are no complaints from the beginning and therefore no complaints are made at the time of recovery so that medical science seems to have nothing to do at all with such local inflammation. The nasopharyngitis has, however very significant effects on the whole body and its treatment throws much new light on a hitherto unknown field of treatment, thus also raises significant problems for us.

This is the main reason that we have been made efforts to establish a practical method of diagnosis.

Inflammations of the nasopharynx exist independently and are for the most part not complicated by inflammation of the adjacent organs such as pharyngitis, rhinitis, etc. In these cases, therefore no inflammatory findings are to be obtained at all simply by observation of the mesopharynx or nasal cavities. Although this fact does not concern directly observation of the nasopharynx, however if we regard the nasopharynx as a part of the pharynx or nasal cavities, the absence of inflammatory changes in the immediately adjacent organs or in seemingly the same organ would normally rule out the existence of nasopharyngeal inflammations. This fact is, though not so important in leading to the diagnosis of nasopharyngitis itself, of much diagnostic significance in cases of nasopharyngitis.

Nasopharyngitis cannot always be sufficiently diagnosed by the otorhinopharyngolaryngological diagnostic methods prevalently applied i.e. by only optical methods such as posterior rhinoscopy nasopharyngoscopy etc. Nasopharyngitis, unlike tumor or adenoids, does not cause morphological changes, its chief manifestation consists for the most part merely of mucosal redness, and findings such as posterior rhinorrhea, etc. are, if they exist at all of relatively rare occurrence. It will easily be understood that correct determination even of a

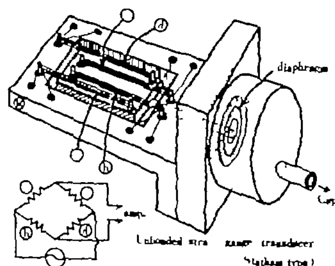
infantile cases much more frequently than in adult cases.

From the above it is clear that the nasopharynx is the most important of the common foci of inflammation.

11 Stimulation of the Nasopharynx and the Autonomic Nervous System

1) Stimulation of the Nasopharynx and Vasomotor Reflex

We have found the fact that the small blood vessels of the fingertip are easily constricted by stimulation of the nasopharyngeal wall (HARADA, 1968). The fingertip volume–pulse wave can be obtained as follows. The changes of the air content in a finger cup put tightly on the fingertip is converted into electric current by a straingauge and amplified to obtain an oscillogram (Figs. 20, 21). Such plethysmographic observations of pulse waves in the fingertip reveal a marked contraction in them during abrasion of the nasopharyngeal walls by nasal or pharyngeal swabs. In normal cases, however, the constriction continues only for 10–30 seconds and returns to its initial value. In Fig. 22, a momentary contraction of the pulse wave is



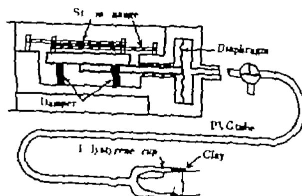


Fig. 20. Pneumatic strain gauge plethysmography

little increase of mucosal redness by optical methods is practically impossible, since the normal mucosa itself is originally reddish in color observation of the redness of the nasopharynx, which can be observed only with difficulty and cannot be sufficiently illuminated is still more difficult. Thus the optical method does not suffice for the perfect understanding of nasopharyngitis. Only direct abrasion can make the diagnosis possible. This is another reason why this disease has been left behind as the subject of medical studies.

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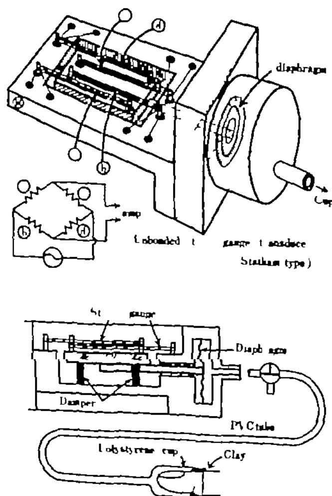


Fig. 20. Pneumatic strain gauge plethysmography



Fig. 21 System block diagram of finger plethysmography

Table 22 Standard value of finger vasomotor reflex.

Duration of reduced amplitude	Cases
10 sec	4
15	10
20	5
30	1

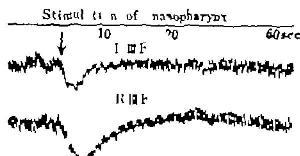


Fig 22. normal finger vasomotor reflex.

shown. Twenty healthy adults without abnormalities in the autonomic nervous system were examined by this method, and the results obtained are given in Table 22

The constriction time of the blood vessels of the fingertip under stimulation of the nasopharynx of 20 healthy subjects was less than 10, up to 15 20 and 30 seconds in 4 10 5 cases and 1 case respectively The normal constriction of the blood vessels of normal subjects under

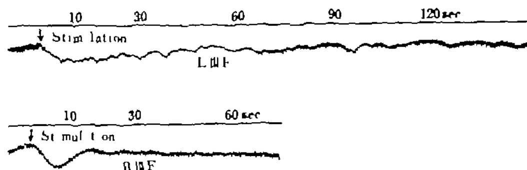


Fig 23. abov Case of prolonged constriction time. down Normal case.

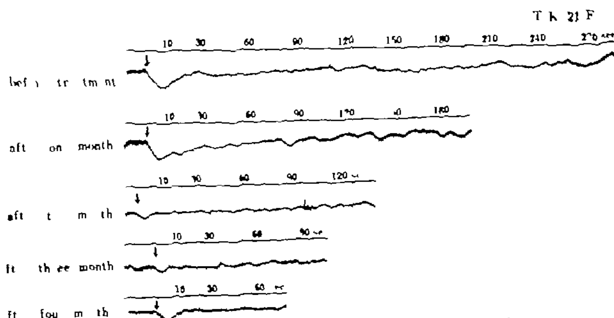


Fig 24. Change of duration of constriction during tre nasopharyngitis.

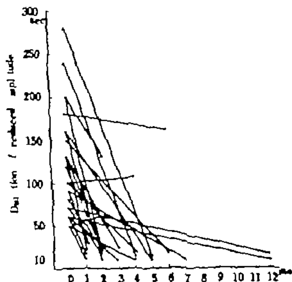


Fig. 23. Changes in finger vasomotor reflex in course of treatment.

nasopharyngeal stimulation was found to last about 15 seconds. In this way the reactions of the pulse waves of the fingertip with nasopharyngeal stimulation in each case were classified, so the constriction time was found to be markedly drawn out some cases beyond the normal limit mentioned above. In one case the constriction time is especially long as compared with that of about 15 seconds in normal cases in Fig. 23. Thus the constriction in certain cases cannot be restored for 60, 120 seconds, and even for 30 minutes or several hours. In such cases the examination reveals surely the presence of a severe nasopharyngitis. Further study has revealed that this elongation of the constriction time is closely related to the so-called autonomic nervous symptoms. Such an elongation of the constriction time can also be improved gradually by local treatment of nasopharyngitis and be restored finally to its normal value of about 15 seconds. An example of such cases is given in Fig. 24: the constriction time of 270 seconds at the first visit was reduced to 180, 120 and 90 seconds 1, 2 and 3 months after the beginning of treatment for nasopharyngitis respectively, and returned to its normal level after treatment for 4 months.

In such cases with abnormal lengthening of digital pulse wave constriction time by nasopharyngeal stimulation, the pulse wave constriction can be normalized by local treatment of nasopharyngitis very frequently and, as shown in Fig. 23, indeed in almost all cases. In Fig. 23 the duration of therapy before restoration of pulse wave and its constriction time are given on the abscissa and the ordinate, respectively. The comparison of the constriction time before and after nasopharyngeal treatment reveals, as shown in Fig. 26, that it has been markedly improved in the latter. These data, though they are the same as in the

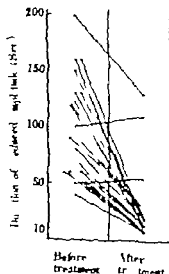


Fig. 26. Restoration of pulse wave after nasopharyngeal local treatment; comparison before and after treatment.



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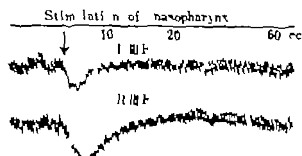


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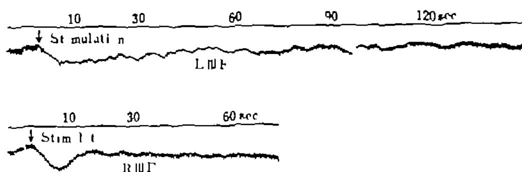


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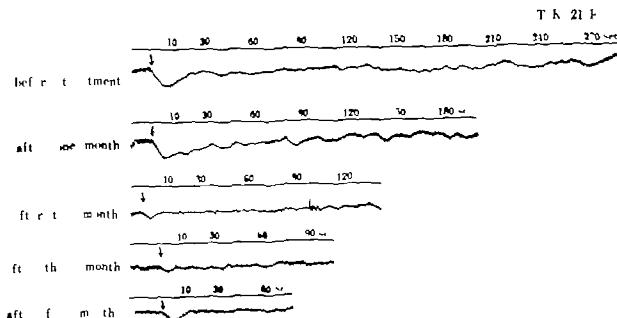


Fig. 24. Change of duration of constriction during treatment of nasopharyngitis.

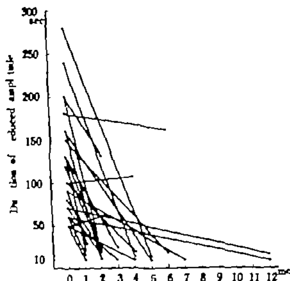


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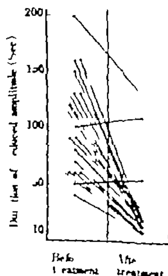


Fig. 26. Restoration of pulse wav after nasopharyngeal local treatment; comparison before and after treatment.

Fig 25 are enough to indicate therapeutic effect.

The fact that the nasopharyngeal stimulation causes a marked constriction of small digital vessels and eventually an abnormal lengthening of the constriction time is of considerable importance.

The constriction of small digital blood vessels through the vasomotor nerve while the autonomic nerve responds to a stimulus. The vascular constriction is probably the result of an adrenergic effect and though the role of the sympathicus and the parasympathicus in the constrictions of blood vessels is not to be discussed here, it is at least certain that nasopharyngeal stimulation will produce considerable effects upon the autonomic nervous system. Through the plethysmography of the digital pulse wave therefore an objective method for determination of the effects of nasopharyngeal stimuli upon the autonomic nervous system has been developed. In cases of normal adults the autonomic nervous system responds to nasopharyngeal stimuli (through the scale of the digital pulse wave) commonly for about 15 seconds but eventually even 30 min or several hours as mentioned before even with stimuli of almost the same degree. Such cases with reaction of long duration are, moreover associated with severe nasopharyngitis without exception

The irritability of the autonomic nerve, being projected into the pulse wave constriction time as objective data makes possible the objective observation of the abnormality of the autonomic nerve and thus indicates certain progress in the field This fact has been realized through the disease nasopharyngitis Another fact of interest is that the normal state of the autonomic nerve can gradually be restored by the treatment of nasopharyngitis The therapeutic effect projected into the vascular motility in cases of nasopharyngitis, though it may not always be under special circumstances can express objectively the functional disorders of the vasomotor nerve and the autonomic nerve and control it consequently in a a sense In this case we are concerned naturally only with the vasomotor nerve however this effect considered together with that upon the blood pressure, as will be mentioned later is certainly a subject of deep interest.

2) Stimulation of the Nasopharynx and the Mecholyl Test

The mecholyl test originated by GELLHORN (1956) is one of the test methods for autonomic nervous function. This method consists in recognizing the functional state of the autonomic nervous system by the patterns of the blood pressure curve, while the systolic blood pressure is successively registered after the injection of a choline derivative, acetyl-β-methylcholine (Mecholyl) OKINAKA (1959 1960) classified these patterns according to the changes of the blood pressure once decreased after the mecholyl injection in any case into 3 types

1 S-type (Sympathetic hyperreactor) the blood pressure which is once decreased begins to increase again becomes 10 mmHg higher than before injection and thereafter returns gradually to its initial value.

2 N type (Normoreactor) the blood pressure, which is once decreased starts to increase, without becoming more than 10 mmHg higher than that before injection and returns to its initial value about 10 minutes after injection.

3 P type (Sympathetic hyporeactor) the blood pressure which is once decreased does not return to its initial value even after 10 minutes and remains decreased.

The S-type and the P type are regarded as abnormal types of autonomic nervous functions. In Fig 27 these processes are shown

It is a well known fact that this mecholyl test is a method for examination of vegetative dystonia Generally vegetative dystonia is mostly of a central nature so its examination methods are mostly psychological tests mainly developed and applied by SIEBECK, HERBST WENGER ABE et al to determine the psychological effects. There have been applied formerly as direct test methods for autonomic nerve function various tests with drugs such as adrenaline, pilocarpine atropine etc.

These tests with drugs as autonomic nerve toxins are not always applicable and can be dangerous when applied in cases with hypersensitivity of the autonomic nerve Are there not, therefore any test methods for functional

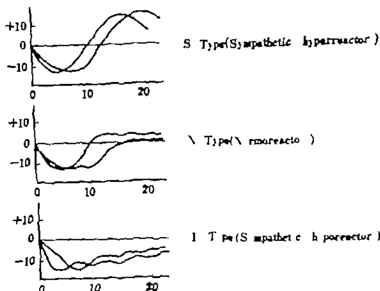


Fig. 27 Three types of Response of Mecholyl Test.

states of the autonomic nervous system without using drugs?

While we have taken notice of the relationship between the digital pulse wave constriction and nasopharyngitis and further nasopharyngeal stimulation and the autonomic nerve, we ha felt interest in the response of blood pressure to nasopharyngeal stimulation instead of the mecholyl injection. On the subjects of each N S- and P-type according to the abov mentioned mecholyl test, the effect of nasopharyngeal stimuli upon blood pressure was observed. The observation of the successive changes of blood pressure was done in the same way as in the mecholyl test. As result, in each case the blood pressure once increased directly after nasopharyngeal stimulation without exception, and thereafter changed in the closely similar way to that after its initial decrease in the mecholyl test. In Fig 28 the changes of blood pressure caused by nasopharyngeal stimuli are given in each N S- and P type of actual cases. The changes of blood pressure caused by nasopharyngeal stimuli are summarized as follows

1 Marked increase immediately after nasopharyngeal stimulation.

2. Three different modes of changes thereafter i.e

3. The blood pressure once increased returns to its initial level before stimulation within almost 2 1/2 min. and alters little thereafter *(this corresponds to the N-type in the mecholyl test)*

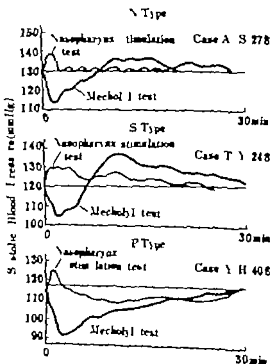


Fig. 28. Nasopharyngeal stimulation and Mecholyl test.

4 The blood pressure increased after the stimuli does not return to its initial value even after 3 min. or more, and increases further for several or scores of minutes (this corresponds to the S-type in the mecholyl test)

5 The blood pressure once increased after the stimuli begins to decrease immediately even beyond the initial level before stimulation and remains at its level for several or scores of minutes (this corresponds to the P type in the mecholyl test)

From these results it can be seen that the effects of nasopharyngeal stimuli resemble closely to those of mecholyl injection. The determination of changes of the blood pressure caused by nasopharyngeal stimulation is useful as a test method compatible with and more convenient than the mecholyl test

3) Vegetative Dystonia and Nasopharyngitis

In order to compare the nasopharynx stimulation blood pressure curve (hereafter referred to as NSBP) mentioned above and the degree of nasopharyngitis, 30 cases of erosive nasopharyngitis of especially marked degree showing post abrasive pain and hemorrhages were selected for determination of NSBP The results obtained are given in Table 23 In serious cases, as seen in Table 23 S- and P type are most frequently seen and the both types together show the high percentage of 80

On the contrary of 10 (seemingly almost normal) cases of slight nasopharyngitis 2 were of S-type and 1 was of P type and 7 cases, i e. the high percentage of 70 were of N type By this fact it has been shown that the degree of nasopharyngitis is, in a sense related with the autonomic nervous disturbances. The types of the autonomic nervous system have hitherto been understood as being classified constitutionally however it is important that it has been elucidated that they are related with the nasopharyngitis, a superficial inflammation occurring a posteriori

Table 23 Cases of nasopharyngitis.

Blood pressure curv	Cases of nasopharyngitis	Cases with normal nasophary
S Type	12 (40)	2 (20)
N Type	6 (20*)	7 (70*)
P Type	12 40%)	1 (10%)

If it is possible for us to normalize the abnormal blood pressure patterns by local treatment of nasopharyngitis, it should be said that it has become possible to control the abnormal autonomic nervous pattern. Regarding such possibilities we have spoken in the previous chapter about the digital pulse wave and further possibilities with regard to NSBP will be mentioned in the next chapter

4) Treatment of Nasopharyngitis and Blood Pressure Curve after Nasopharynx Stimulation

The above blood pressure curve obtained after nasopharyngeal stimulation can be as after the mecholyl injection regarded as a manifestation of the blood pressure pattern of the autonomic nerve and it is also possible in this case as in the previous case of the digital pulse wave to convert an abnormal pattern to a normal one by prolonged treatment of the nasopharynx. *Fig 29 a.* shows the method of stimulating or treatment of nasopharynx. Fig 29 shows the case of a 59 year-old male treated in this way His chief complaint at the first examination was *headache* (headache and nasopharyngitis are closely related with each other as will be mentioned in detail in the pertinent paragraph)

At the first visit in this case local pain and postabrasive hemorrhages were marked at abrasion of the nasopharynx The local pain and the chief complaint disappeared after treatment of 1 and 2 months duration respectively and the NSBP observed together changed as follows The NSBP was S-type at the time of abrasion P type after one month and N type *after 2 months.* In this case the result of the mecholyl test was S-type in the initial stage with NSBP of S-type The result of the mecholyl test two months after the treatment for nasopharynx was found to be changed into N type In this case the digital pulse wave was not observed. In the other cases, in which the digital pulse wave contriction was prolonged in those with NSBP of P and S-type and when the NSBP become N type after treatment the pulse wave returned also to its normal value In this case therefore the S-type in the beginning changed into the N type after 2 months of the treatment of the simultaneously but latently

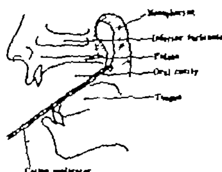
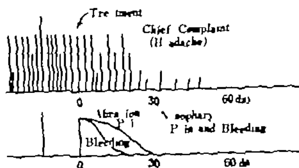


Fig. 29 a. Method of stimulating or treatment.



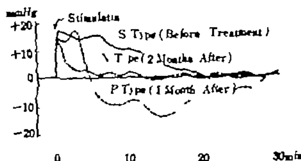


Fig. 29 b. Case K. S., 39, M.

Table 24. Cases of Nasopharyngitis

Case	Age	Sex	Blood pressure curv.	
			Before treatment	After treatment
1	19	F	N	N
2	23	F	S	N
3	39	F	P	N
4	34	F	S	N
5	32	F	S	N
6	27	M	N	N
7	33	F	P	N
8	13	M	S	N
9	54	F	P	N
10	24	M	S	N
11	30	M	S	N
12	19	F	P	N
13	16	M	P	N
14	38	F	N	N
15	20	F	P	N
16	45	M	N	N
17	66	M	P	N
18	45	F	P	S
19	60	M	S	N
20	40	M	P	N
21	28	F	S	N
22	33	F	P	N
23	38	M	S	N
24	28	F	S	N
25	23	F	S	N
26	31	F	P	N
27	23	F	P	N
28	48	F	S	N
29	25	F	N	N
30	17	M	S	N

Table 25. Effect of nasopharyngitis treatment.

Type of blood pressure curv.	Treatment of nasopharyngitis	
	Before	After
S Type	12 (40%)	1 (3%)
N Type	6 (20%)	29 (97%)
P Type	12 (40%)	0 (0%)

existing nasopharyngitis.

The constitution has been regarded as a conclusive factor in determining the type of the autonomic nerve, which can be altered temporarily but not permanently by administration of drugs. however It was found that such an *abnormal type can be changed into the normal* type by local treatment of a hidden inflammation, nasopharyngitis, as shown in Tables 24 and 25. The local treatment for nasopharynx was done daily in 30 cases of severe nasopharyngitis, as is shown in the tables, and 24 and 6 cases were of abnormal and normal type before treatment, respectively after treatment the abnormal type was found only in one case and all the other 29 cases returned to the normal type.

In these healed cases the type remained normal for a fairly long period after a prolonged treatment, and this aspect awaits clarification

through detailed studies in the future. If recurrent acute exacerbation of nasopharyngitis occasionally due to a cold occurs during the course of improvement the blood pressure curve often becomes abnormal but it returns to the normal curve easily after another treatment of the nasopharynx. This aspect applies also to the digital pulse wave mentioned above

The mecholyl test has been applied for detection of the autonomic nervous disorders, and the results have been useful as a subsidiary method or a conclusive factor for psychological examination of various autonomic nervous functions however the mecholyl itself is often thought to be dangerous since it affects at times deeply the autonomic nervous mechanism. On the contrary nasopharyngeal stimulation is not only not dangerous, but also as effective as mecholyl so it could be available in the future for functional examination of the autonomic nerve

5) Control of the Autonomic Nerve

In the chapters on the digital pulse wave and the nasopharynx stimulation blood pressure curve it was stated that the blood vessel motility and the blood pressure are related very closely with the nasopharyngitis and therefore the nasopharyngeal stimulation makes possible the examining of the functional state normal and abnormal of the autonomic nerve Furthermore the abnormal state of the autonomic nerve revealed by these examinations was restored gradually by treatment of the nasopharynx, and the restored state remained semipermanently

It is a very interesting fact that an abnormal state of the autonomic nerve can be returned to its initial normal state by treatment of nasopharyngitis. It has been previously impossible for us to restore the autonomic nerve in its abnormal state to the normal state The autonomic nerve in the abnormal state could be restored e g by administration of certain drugs, not permanently but only temporarily The abnormality of the autonomic nerve has been therefore regarded not as a state but as a constitutional and permanent feature The autonomic nervous disturbances have been considered as a state not to be controlled by man. It is an interesting fact that the local treatment of nasopharyngitis made it possible to restore the autonomic nervous disturbances regarded as uncontrollable

The autonomic nervous disturbance manifests generally various symptoms. This abnormal state is, moreover situated between the soul and body so it will be considered as of psychogenic or of purely organic nature. For instance headache or palpitation will belong to the soul (in the present paper headache is not considered as a state influenced by the autonomic nerve) but the changes such as gastric ulcer etc. are probably organic changes pertaining to the body To study the possible relationship between the autonomic nerve and a certain disease the carriers of the disease have commonly been tested for a hypersensitive state of the autonomic nerve. Such a state of the autonomic nerve can be tested in two ways, namely by psychological examination and by a response test after injection of autonomic nerve toxins. The methods of SIEBECK (1939) HERBST WENGER (1947) etc. and in Japan, of IKEMI (1966) ABE (1960) etc are regarded as the former All of these methods consist in psychological examination requiring answers to various questions. On the contrary these are tests for toxicity of drugs, such as adrenaline, pilocarpin atropine noradrenaline mecholyl etc. and these for response to the direct physical stimuli such as ASCHNER s method CZERMAK HERING s method, cold pressor test test through change of position, etc. or dermography There are so many test methods used because the response to the stimuli is not always stable while various methods including the psychological one indicate that the autonomic nervous system is unconditionally and inevitably controlled by the central nervous system.

The cause for this unstability will be attributed to the fact that the autonomic nerve is not always in a stable state but is, especially in the so-called 'neurotic patients, in an exceedingly changeable state correspondingly regulated by the central nervous system, so it remains difficult to understand its pathological features by examination.

This problem is to be solved only by possible restoration of the autonomic nerve to a stable state In this sense the normalization of the above mentioned abnormal state of the auto-

nomic nerve by nasopharyngeal treatment has certainly enlarged our biological knowledge of the autonomic nerve. In the following we want to observe how the patients with various complaints, the so-called autonomic nervous symptoms stated in the above, can be improved by nasopharyngeal treatment.

As the so-called autonomic nervous symptoms, Siebeck has indicated various signs, from which we have selected the following ten as main symptoms. Each of these symptoms is present frequently as a separate or compound complaint and can be improved by nasopharyngeal treatment with marked response. There will be given in detail in the following such symptoms, of which e.g. headache, dizziness, diarrhea, gastric ulcer etc. are representative. The 10 main symptoms are as follows:

- i. Cutaneous symptoms: 1. cold feeling 2. hot feeling 3. abnormal secretion
- ii. Cardiac symptoms: 4. palpitation 5. pulsus celer unstable pulse
- iii. Vascular symptoms: 6. dizziness 7. migraine 8. variable blood pressure
- iv. Gastrointestinal symptoms: 9. constipation 10. diarrhea

The patients with a so-called neurosis generally have many such complaints. Such autonomic nervous complaints have been regarded as complaints without any known cause and being probably of psychogenic origin, so that administration of psychostatic drugs or psychotherapy has been done without its being a definite treatment. The observation of the prolongation of the digital pulse wave constriction time caused by the previously mentioned nasopharyngeal stimulation, especially upon the patients with the above mentioned neurotic complaints, reveals positive prolongation of the digital pulse wave constriction time in most cases.

So far as the vasomotor nerve of the peripheral blood vessels is concerned, the hypersensitivity of autonomic nerve was often found in patients with neurotic symptoms. So we have observed many of these patients, as shown in Table 26 and attempted to compare the digital pulse wave constriction time under nasopharyngeal stimulation with the number of autonomic nervous symptoms indicated by Siebeck as above (e.g.

Table 26 Relation between finger vasomotor reflex and autonomic nervous symptoms

Duration of reduced amplitude	Autonomic nervous symptoms									
	Number of positive symptoms									
	1	2	3	4	5	6	7	8	9	10
> 30 sec	7	7	3							
30–59	1	1		2						
60–119			2	7	4	1	1			
120–300			2	2	3	2	2	1		
300 <					1		1			

3 if a patient complains of cold feeling in the skin, dizziness and migraine).

The number of complaints and the period of prolongation (sec) of the pulse wave have been compared with each other. This comparison has revealed that there is a close correlation between the prolongation of the pulse wave constriction time caused by nasopharyngeal stimulation and the number of complaints of the patient. To this correlation much significance can be attached, so the autonomic nervous symptoms regarded hitherto as of psychogenic origin are in fact not always of psychogenic origin but also projected considerably into the (so to speak organic) pathological changes of the autonomic nerve itself. This has been realized only through stimulating the nasopharynx, and, in fact, has proved the possibility of replacing at least the psychogenic, completely intractable phenomena with the autonomic nerve as a more or less objective matter.

In the previous chapter it was indicated that the constriction of the digital pulse wave caused by nasopharyngeal stimulation and the abnormalities in the blood pressure curve after stimulation can be restored by local treatment of nasopharyngitis in the majority of cases. Is it not possible to apply this fact to the relationship between the prolongation of the pulse wave and the autonomic nervous symptoms (complaints)? The various kinds of autonomic nervous symptoms such as headache, dizziness and others are almost always accompanied by nasopharyngitis and most of these essentially autonomic nervous symptoms have been known to disappear during local therapy for nasopharyngitis as the nasopharyngitis improves. If prolongation of the pulse wave and autonomic nervous disturbance coexist in one and

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the same person and both can be restored by the treatment of nasopharyngitis, objective studies on the autonomic nervous symptoms become possible.

From this viewpoint the patients with many complaints were subjected to observation of the prolongation of pulse wave caused by nasopharyngeal stimulation and at the same time the parallelism between the changes of pulse wave and the improvement in complaints was observed during nasopharyngeal treatment in these cases. Two typical cases will be referred to in the following

Case (Table 27 Fig 30)

T Y 59y ♂

Chief complaint

1 Susceptibility to eczema
2 Palpitation
3 Unstable pulsus tardus or celer
4 Migraine on the left side
5 Dizziness
6. Tendency toward constipation

In this case, in short 6 autonomic nervous symptoms are complained of. Observation of the nasopharynx revealed marked inflammation and the abrasion by swabs caused severe pain and profuse postabrasive hemorrhage. In the smears numerous ciliated cells (compatible with desquamation of many epithelial cells) were found which were, however almost normal in their shape, and yet the goblet cells were increased and the appearance of polymorphonuclear leucocytes, lymphocytes, etc. was marked. The prolongation of the pulse wave caused by nasopharyngeal stimulation extended over a period of 160 sec. In the course of treatment of the nasopharynx in this case, as shown in Table 27 and Fig 30 every complaint was gradually improved. The conditions such as palpitation, unstable pulse wave etc. were remedied and the dizziness disappeared one month after the beginning of treatment. Tendency toward constipation disappeared and the patient having a bowel movement every day was in great good humor At this time the prolongation of pulse wave was restored to its normal value of 20 sec. however the patient caught a cold early in the second month and the palpitation reappeared. At this time the pulse wave was again prolonged up to

T ble 27 T Y 59 y.o. M

Duration of treatment (mon)	Autonomic nerve symptoms				Duration of reduced amplitude in plethysmogram at finger tip
	Skin	H rt	Blood vessel	Gastro-intestinal tract	
0	Eczema	Palpitation Pulsus tardus Pulsus frequens	Vertigo or dizziness Migraine	Constipation	160 Sec
1	Eczema	/	Migraine	/	20 Sec
2	Eczema	Palpitation	Migraine	/	60 Sec
3	Eczema	/	/	/	15 Sec
4	/	/	/	/	15 Sec
5	/	/	/	/	15 Sec

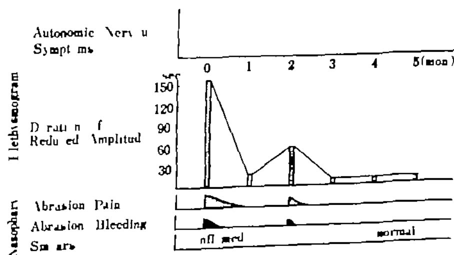


Fig. 30. Case T Y 59 y.o. M

60 sec. and nasopharyngeal abrasion caused again abrasion pain and postabrasion hemorrhage, which had once completely disappeared. During further treatment of the nasopharynx these acute symptoms disappeared soon, and the nervous symptoms were *also improved gradually* and in the 3rd month the symptoms such as palpitation and migraine, disappeared completely leaving only the eczema.

The pulse wave returned to its normal level of 10 sec. In the 4th month the eczema also disappeared and the *autonomic nervous symptoms* disappeared completely. Since then the pulse wave has remained at 10 sec. and no autonomic nervous symptoms have *been found.*

The symptoms such as headache, dizziness, eczema, etc. often showing a marked improvement equally by the nasopharyngeal treatment, *were found to be improved in parallel to the* prolongation of the pulse wave constriction time. Practically *through the nasopharyngeal* treatment it can be understood that the improvement of such autonomic nervous symptoms covers a wider range. *For instance if a* feeling of impatience, called hysteric stigmata, or *of general fatigue associated with the above* mentioned complaints was treated by nasopharyngeal therapy these feelings can frequently be improved according as those symptoms disappear. In cases only with feeling of fatigue or impatience furthermore, the nasopharyngeal treatment can often produce certain effects. A case of a female patient with such complaints, treated as hysteria, will be given in the following.

Case (Table 28, Fig. 31)

R.K. 26 y ♀

Chief complaint: Posterior rhinorrhea, general fatigue.

Persistent posterior rhinorrhea after cold caught about 10 years before. Treatment of rhinitis at an ENT clinic the following year. Resultant aggravation rather than improvement. Posterior rhinorrhea, general fatigue, feeling of *general coldness, palpitation since* month

Table 28 Case R.K. 26 y.a. F

Duration of treatment (Week)	Autonomic nervous symptoms				Duration of reduced amplitude in plethysmogram at finger tip
	Skin	Heart	Blood vessel	Gastro-intestinal tract	
0	Cold feeling	Palpitation	Vertigo	Constipation or Diarrhoea	240 Sec
3	Cold feeling	/	/	Constipation or Diarrhoea	135 Sec
6	Cold feeling	/	/	Constipation or Diarrhoea	110 Sec
9	/	/	/	Constipation	60 Sec
13	/	/	/	Constipation	15 Sec
16	/	/	/	Constipation	15 Sec

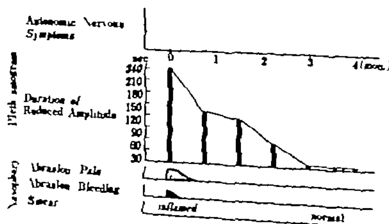


Fig. 31.

the same person and both can be restored by the treatment of nasopharyngitis objective studies on the autonomic nervous symptoms become possible

From this viewpoint the patients with many complaints were subjected to observation of the prolongation of pulse wave caused by nasopharyngeal stimulation and at the same time, the parallelism between the changes of pulse wave and the improvement in complaints was observed during nasopharyngeal treatment in these cases. Two typical cases will be referred to in the following

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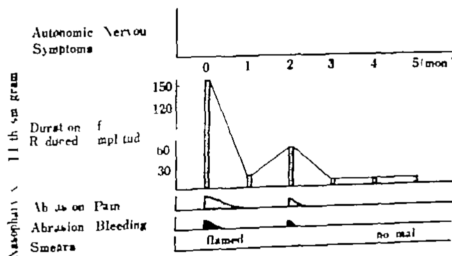


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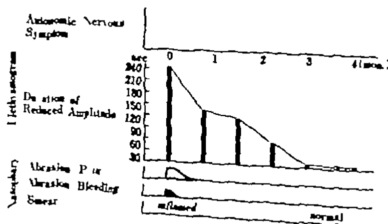


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the same person and both can be restored by the treatment of nasopharyngitis objective studies on the autonomic nervous symptoms become possible

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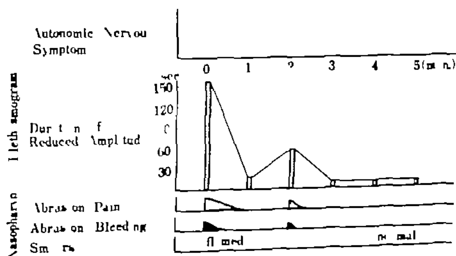


Fig 30. Case T Y 59 y.o. M.

Table 29 Comparison before and after chlorpromazine injection.

Case	Age	Sex	Plethysmography		Type of blood pressure curv.	
			Before	After	Before	After
1	25	F	60 sec.	0 sec.	P	N
2	33	M	15	5	N	N
3	50	F	100	0	S	N
4	30	F	cont.	10	P	N
5	16	M	80	5	S	N
6	31	F	300	0	S	N
7	32	M	cont.	0	N	N
8	30	F	400	5	S	N
9	40	F	20	0	S	N
10	38	M	120	0	P	N

tion before and after chlorpromazine i jection are given in each left and right half of the left column, respectively The digital pulse wave was in all 8 cases, except 2 (15 sec. 20 sec.) w thin the normal limits, extraordinarily prolonged. The cases in which the pulse wave constriction extended over a long period of time without being restored during the period of observ tion, are indicated n the column by cont In these cases, however administration of chlorpromazine caused almost no constriction and even the nasopharyngeal stimula tion was unable to produce changes in the pulse w e. There were found n a few cases certain changes, which were always within the normal limits. In the right column the changes of blood pressure after the nasopharyngeal stimulation are set down the changes before and after the injection of chlorpromazine on the left and right side, respectively Namely the changes of blood pressure following nasopharyngeal stimulation before the injection were of abnormal type S or P except in 2 cases of N type however after the injection of chlorpromazine the changes of blood pressure following nasopharyngeal stimulation were of N-type without exception. It appears to be fairly well established from this experiment, that the presence of nasopharyngitis is very closely related to the autonomic nervous system.

Note 1

The digital cup has capacity of 14cc, an inside diameter of 20mm and an outside diameter of 22mm and is made of polyvinyl chloride. The middle finger is introduced into the cup, and its proximal end is fixed with clay so that the introduced finger will be made completely airtight.

The cup and the transducer (strain gauge) are connected ith each other by polyvinyl tube having an inside diameter of 3mm and thickness of about 1mm. The polyvinyl tube should be, though flexible free of elasticity

Note 2

The downward shift of the pulse curv means decrease of blood flow and the decrease of pulse amplitude, decrease of pulse pressure. In short this indicates the reduction of diameter of the peripheral blood vessels.

before consultation.
Diagnosis of neurosis at the internal clinic.
Findings at the first examination.
Autonomic nervous symptoms 1 coldness in the extremities, 2 palpitation, 3 dizziness, 4 constipation 5 diarrhea
Pulse wave constriction time 240 sec.
Nasopharyngeal findings.
Severe pain and postabrasive hemorrhages at the time of nasopharyngeal abrasion with pharyngeal swabs. There could be found in the smears from the abrasion specimen numerous ciliated epithelial cells with obscure ciliary structure, indistinct cuticular border and markedly swollen cytoplasma and a moderate number of wandering cells such as leucocytes, lymphocytes, etc.
Disappearance of abrasion pain and postabrasive hemorrhages of the nasopharyngeal wall within 6 weeks after the beginning of treatment. At that time excess general fatigue was found immediately after the beginning of treatment so that even standing was not endurable, but this was improved rapidly by further treatment. Movement was subjectively improved in the first week and in the second week the patient was further improved and even became highly energetic. Disappearance of palpitation and dizziness in the sixth week of treatment. Simultaneous decrease of the pulse wave constriction time to 110 sec. Furthermore in the third month of the treatment, complete disappearance of inflammatory features in the smears from the nasopharynx, and of all autonomic nervous symptoms except constipation, and restoration of the pulse wave constriction to a normal value of 15 sec.

In the above cases severe fatigue was improved of the cases with disturbances such as irritability however there are often also cases restored by the treatment of nasopharyngitis. In this connection it is interesting to note that a certain case of orthostatic regulatory disturbance was improved by treatment for nasopharynx, while the child in this case became lively and even the abnormalities of the patient's character such as late rising dislike of school fickleness etc were improved A matter of further interest is the masked depression. This means a depression occurring in association with rheumatism or hypertension and is not a true psychosis however this disease as well as the associated rheumatism or hypertension is possibly related to nasopharyngitis. From this possibility it may further be expected that nasopharyngitis without rheumatism or hypertension leads only to depression Under the conditions immediately after the treatment of nasopharyngitis the constriction of the digital blood vessels occurs, as mentioned already and in certain cases, the intracerebral blood vessels are also supposed to be particularly susceptible to this treatment. This possibility is suggested also by the constriction of the basilar blood vessels, while most patients complain of markedly decreased thinking power and drowsiness immediately after treatment Afterward however the patients become especially clear headed for a considerably long period On the basis of the possibility of such alterations in the small blood vessels of the brain we have also carried out a study of the constriction of the larger blood vessels of the brain on which it will be detailed later As a problem, what sort of relation is borne by the constriction of the digital pulse wave caused by nasopharyngeal stimulation to the variation of blood pressure (NSBP) immediately after stimulation? A close relationship between them may exist and its mechanism requires further study

Chlorpromazine Injection

The response of the autonomic nerve to nasopharyngeal stimulation and the effect of the treatment of nasopharyngitis on the autonomic nervous disturbance are referred to just above and what kind of variety will be given to abnormal states of the autonomic nerve detected through nasopharyngeal stimualtion by drugs? In this connection there have been observed the reactions caused by adrenaline noradrenaline, acetylcholin, chlorpromazine etc of which those caused by chlorpromazine were most interesting On 10 patients with autonomic nervous disturbances treatment with *i.m.* injection of 0 5mg/kg chlorpromazine and nasopharyngeal stimulations was performed before and after which the variation of the blood pressure and the digital pulse wave were studied On these patients preliminary studies on neurovegetative conditions (NSBP and pulse wave) before administration of drugs had been performed by stimulating the nasopharynx.

In the left and right column of Table 29 the digital pulse wave and the variation of blood pressure are set down. Changes of the digital pulse wave caused by nasopharyngeal stimula

ELT thus determined. As remarkable changes of ELT were observed when the nasopharynx was irritated ELT in Fig 32 was determined without irritating the nasopharynx before taking blood. However diagnosis of the nasopharynx can be done correctly only by abrasion of the nasopharyngeal mucosa. Therefore the nasopharyngeal mucosa was abrased in all patients after blood letting and it was decided whether they had nasopharyngitis by

1. abrasion pain
2. postabrasive hemorrhage, and
3. examination of the smears.

Those in whom the absence of inflammation could be determined according to the above standards were taken as controls and compared with those with nasopharyngitis. As shown in Fig 32, ELT of controls was from 150 to 200 minutes, while in the group with nasopharyngitis, ELT varied extremely ranging from 50 to 500 minutes.

To study what this result suggested, patients with nasopharyngitis were divided into 3 groups, namely acute, subacute and chronic, and ELT of these 3 groups was investigated. (Acute nasopharyngitis was the stage of dry feeling of dorsal surface of the soft palate and slight rhinolalia aperta (open nasal voice). When touched with cotton applicator marked abrasion pain and bleeding were caused in the nasopharynx, and in the examination of the smears severe inflammation, namely significant transformation of the epithelial cells, and the appearance of wandering cells and various bacteria were observed. The most characteristic symptoms among these were abnormal feeling of nasopharynx and open nasal voice accompanied with so-called cold symptoms. Subacute nasopharyngitis is stage of the disease where local symptoms of acute nasopharyngitis disappear. Even after local symptoms disappear an inflammatory condition often remains continuously without any subjective symptoms. As mentioned before, this kind of inflammation is present in many persons. A chief complaint of chronic nasopharyngitis was postnasal discharge, which was caused by pus excreted from the nasopharyngeal mucosa itself and not by sinusitis. Those with chronic nasopharyngitis did not feel much abrasion pain in the nasopharynx. In spite of that significant changes were observed in the examination of the smears, such as transformation and desquamation of the epithelial cells and wandering of neutrophiles and lymphocytes. This is an outline of classification of the 3 types of nasopharyngitis.)

Fig 33 shows ELT corresponding to the 3 types of nasopharyngitis classified according to

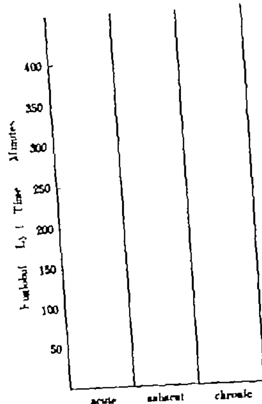


Fig. 33.

the above standards. From these results it is seen that ELTs of acute nasopharyngitis were shorter than 200 minutes, most of them being around 100 minutes ELT of chronic nasopharyngitis were longer than 200 minutes, mostly around 300 to 350 minutes and ELTs of subacute nasopharyngitis were in between. In other words there was characteristic difference in ELT between acute and chronic nasopharyngitis. ELT of subacute nasopharyngitis were similar to those of the normal subjects shown in Fig 33 and they might belong to either the acute or the chronic group.

From these results it became clear that ELT changed according to the condition of nasopharyngeal inflammation. It was even more interesting to know that ELT changed after stimulating the nasopharynx as shown in Fig 34 ELT of blood taken before stimulation of nasopharynx was 175 minutes, but ELT determined 15 minutes after stimulation, which was performed immediately after blood taking, was shortened to 135 minutes and ELT recovered to

12 Nasopharyngeal Stimulation and Alteration of the Body Fluids

In the preceding paragraph it was mentioned that stimulation of the nasopharynx had significant influence on the autonomic nervous system It is well known that changes in the condition of the autonomic nervous system bring alteration of catecholamine cholin and various other body fluids. And it is easily supposed that alteration of various body fluids is also caused secondarily by this.

Considering these possibilities the author studied what influence nasopharyngeal stimulation had on the body fluids. From clinical necessity studies were first conducted on the following items.

1 Alteration of fibrinolytic activity
2 Alteration of plasma 11 OHCS
3 Alteration of γ-globulin
4 Alteration of free fatty acid in plasma

Putting aside how these are related to catecholamine cholin or the autonomic nerve center mentioned before, the experiments conducted on the above 4 items by the author are reported below

1) Alteration of Fibrinolytic Activity

Blood coagulates when it comes out of the body through bleeding If this coagulated clot is left as it is it starts to dissolve again after a while This phenomenon is called fibrinolysis of blood It is known that this phenomenon is accelerated by stress. When there is acute inflammation in the body or a rheumatic attack this fibrinolysis is accelerated If that is the case what kind of correlation exists between this fibrinolysis and the nasopharynx, in which an inflammatory condition is constantly found in many cases?

To study this the author determined the fibrinolysis of blood from patients with nasopharyngitis and those without nasopharyngitis (those with no significant inflammatory changes when nasopharyngeal tests were conducted) (In both groups only those who had never experienced nasopharyngeal treatment were used.) BUCKELL's method was used as shown below

1 0.5 ml of 0.1 ammonium oxalate solution and 4.5ml of blood were mixed.
2 Serum was separated by centrifuging the mixture at 3 000rpm for 5 minutes. The supernatant was discarded.
4 The precipitate was dissolved in 0.5ml of 0.5* borate buffer in a water bath kept at 37°C 0.5ml of 0 025M $CaCl_2$ was added to it to stimulate stimulate coagulation and the time needed for coagulation was determined.
5 The time needed for dissolution of the serum was determined.

As shown above Euglobulin Lysis Time (ELT) was determined Fig 32 shows the

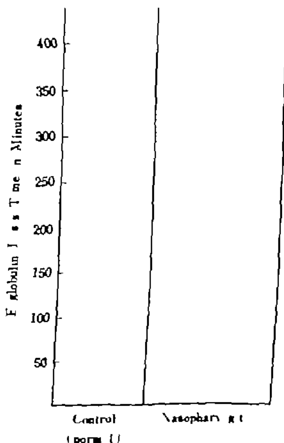


Fig. 32.

than in acute and subacute nasopharyngitis not only the decrease of ELT after 15 minutes was less but also its recovery was remarkable and it had already returned to close to the normal value after 90 minutes. On the contrary, in acute nasopharyngitis, ELT was shortened significantly by stimulation, about 70% after 15 minutes, and only in a few cases was ELT restored to the level before stimulation after 90 minutes; most ELT stayed at 70% to 80%.

What kind of factors caused such differences in ELT between acute and chronic nasopharyngitis is a serious problem and needs to be solved in the future. In acute nasopharyngitis, abrasion of the nasopharyngeal mucosa by a cotton applicator often caused severe pain, while in chronic nasopharyngitis it hardly caused pain. Therefore this difference in ELT between acute and chronic nasopharyngitis was possibly thought due to difference in stress, namely abrasion pain. When ELT was determined on treating after radical operation on the middle ear which was accompanied with severe pain, as a control, values like those obtained in acute nasopharyngitis were not necessarily obtained. This finding suggested that changes of ELT after stimulation of nasopharynx were not caused only by differences in abrasion pain.

When local treatment of an inflamed nasopharynx was performed, inflammation was cured relatively easily; hemorrhage on abrasion disappeared after 1 to 2 weeks, abrasion pain disappeared after 2 to 3 weeks and smears also showed a normal picture. ELT at this stage, however, showed significant difference when compared with that determined before the treatment. (For the treatment 1 to 2% $ZnCl_2$ solution was applied to the nasopharynx every day or every other day. ELT was tested before and after application of 1 to 2% $ZnCl_2$ solution. As the same treatment as that which has been performed every day was performed before and after the ELT test, habituation came into question. However, when nasopharyngitis took a

Table 50 Fibrinolytic activity of one Case

	ELT			Change	
	Control	15 min	90 min	15 min	90 min
Before treatment	99	67	90	67.7	90.9*
After treatment	144	125	129	86.8	89.6

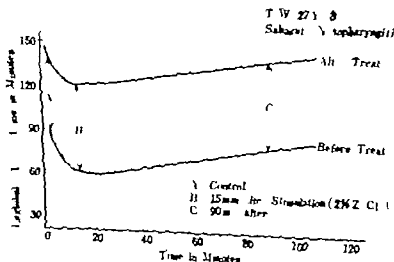


Fig. 30. Case observation (Induction of fibrinolytic activity by stimulation of the nasopharynx of one case)

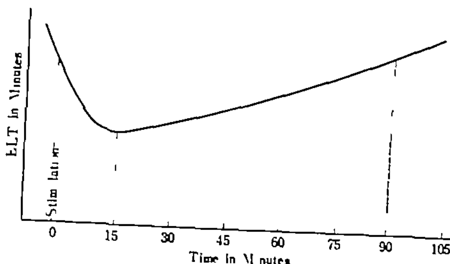


Fig 34. Schema of Progress of Fibrinolytic Activity

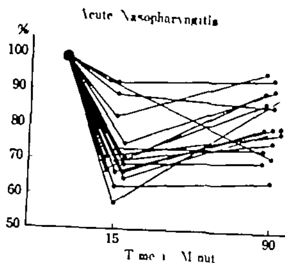


Fig. 35.

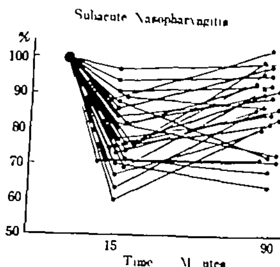


Fig 37

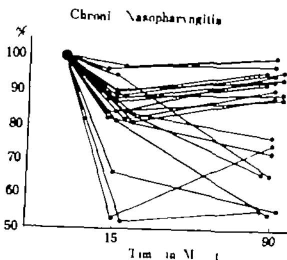


Fig 36.

160 minutes 90 minutes after stimulation The phenomenon that ELT was shortened temporarily after stimulation of the nasopharynx, was common to all subject and ELT reached its minimum value about 15 minutes after stimulation of the nasopharynx and returned to the original value after 90 minutes or more. The minimum value obtained 15 minutes after stimulation and the state of recovery were different depending on the case when these were observed separately Figs. 35 36 and 37 show ELTs determined by stimulating the nasopharynx of the patients with acute chronic and subacute nasopharyngitis. Taking the value before stimulation as 100 ELTs 15 and 90 minutes after stimulation are shown in these figures, which show that the reaction of ELT to stimulation of the nasopharynx was different depending on the individual case

In chronic nasopharyngitis (Fig 36) the effect of stimulating the nasopharynx was less

Table 31 Results.

Case	Name	Age	Sex	Nasopharynx		Plasma 11-OHCS ((γ/dl)		
				Pain	Bleeding	Before	After	Change
1	T.H.	42	F	+	−	16.7	19.2	15%
2	H.H.	25	M	+	−	20.2	20.2	0
3	M.G.	20	F	++	−	19.0	28.5	50
4	Y.K.	29	F	+	−	34.6	23.1	−33
5	K.S.	27	F	+	−	25.8	22.8	−12
6	K.T	28	M	++	±	14.2	20.2	41
7	S.W	28	M	++	+	15.3	21.4	40
8	W.T	33	F	++	+	11.5	18.3	59
9	Y.S.	19	M	++	+	13.0	20.4	57
10	T.O.	58	F	++	++	10.0	14.0	40
11	Y.H.	20	F	+	−	20.0	23.5	18
12	K.N	19	M	+	−	15.0	16.7	11
13	Y.S.	16	F	+	±	10.4	13.5	30
14	E.K.	20	F	++	+	13.0	18.0	39
15	Y.T	[illegible]	F	[illegible]	++	6.1	19.5	220
16	I.S	29	M	+	±	17.5	17.5	0
17	Y.T	28	M	++	+	19.4	29.0	50
18	T.W	20	F	++	+	30.8	28.9	− 6
19	N.K.	38	M	++	++	13.0	21.0	62
20	K.T	32	M	+	−	24.0	12.0	−50
21	M.L	26	M	±	−	19.7	19.7	0
22	H.A.	43	F	++	++	15.0	27.5	83
23	M.S.	46	F	+	+	18.0	22.0	22
24	T.Y	51	M	+	−	18.3	22.1	21
25	K.O.	26	F	+	−	22.1	29.8	35
26	N.M.	62	F	++	+	23.4	30.0	28
27	M.S	53	F	+	−	27.5	30.0	9
28	G.G.	18	M	+	−	32.5	27.5	−15
29	M.Y	52	M	[illegible]	[illegible]	18.8	43.8	133
30	T.T	42	M	++	−	25.5	40.0	57
31	H.H.	41	F	+	−	16.4	20.0	22
32	Y.N.	33	F	++	−	14.6	14.6	0
33	H.M.	41	M	++	−	33.3	12.5	−63
34	J.M.	33	F	++	++	7.1	10.8	52
35	A.K.	31	M	++	+	13.4	12.5	− 7
36	H.M.	12	F	++	++	20.0	5.0	−75
37	T.F	49	F	+	±	11.0	11.0	0
38	Y.T	58	F	++	[illegible]	15.0	22.5	50
39	M.N.	58	M	+	+	27.5	33.5	22
40	H.S	16	F	+	−	20.7	10.3	−50
41	K.K.	40	F	+	−	32.5	37.5	15
42	K.A.	38	M	+	−	31.4	33.0	5
43	K.H.	56	M	+	+	33.3	29.7	−11
44	Y.N	8	F	++	++	18.6	30.0	60
45	T.W	20	F	++	−	21.9	26.0	19
46	K.O.	38	M	+	+	18.3	22.5	23
47	T.O	40	F	+	+	18.3	18.3	0
48	M.M.	37	F	++	+	14.8	21.3	44
49	M.I	28	M	±	−	19.7	19.7	0
50	M.Y	52	F	++	++	22.2	38.8	75
51	H.K.	16	M	++	+	16.0	23.0	40
52	Y.K.	30	F	+	−	22.5	27.5	22
53	M.K.	32	F	++	++	16.7	22.9	37

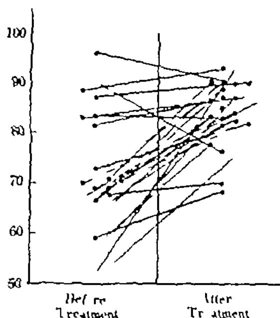


Fig 39

serious turn because of a cold in spite of continuation of the treatment ELT also moved backwards. Therefore there seemed to be no habituation phenomenon.)

Typical ELT curves before and after the treatment of the nasopharynx were shown in *Table 30 and Fig 38*. In these cases ELT after the treatment became significantly longer compared to that before the treatment. Those cases whose *ELT* was prolonged by the nasopharyngeal treatment has short ELT in other *words they had acute or subacute nasopharyngitis*. In chronic patients ELT was shortened or was not changed by the treatment. Fig 39 *showed ELT* values 15 minutes after stimulation of nasopharynx in chronic patients. It was observed that there eas a tendency for ELT to remain at a constant value during the nasopharyngeal treatment

2) Alteration of Plasma 11 OHCS

It is a fact that rheumatism and allergy can be healed or improved very successfully only by local treatment of the nasopharynx. Why has such an effect of nasopharyngeal treatment been elucidated yet? As mentioned before inflammatory foci always exist in the nasopharynx and this inflammation becomes severe in case of rheumatism or allergy. Treatment of this inflammation runs parallel to treatment of these original diseases. In rheumatism, for example nasopharyngitis has the necessary and sufficient conditions to act as a source of focal infection and also in the incipient stage of nasal allergy or asthma an abnormal feeling in the nasopharynx appears first as a premonitory symptom. And so it is most important to treat nasopharyngitis, which is one of the sources of these diseases, and to keep it from participating in their attack. It is very important to study their relation further for investigation of a mechanism of inflammation and allergy

To investigate the mechanism of causal relation between nasopharyngitis and these diseases, the relationships between nasopharyngitis and *ELT* and between nasopharyngitis and the autonomic nervous system have been studied and reported. It is known that ELT is accerlated in proportion to aggravation of inflammation in case of rheumatism and a kind of abnormality in a mechanism of autonomic nerve has an important relation to acceleration or disappearance of inflammation.

It is also clear that an accelerated condition of ELT and an abnormal condition of the autonomic nerve and parallel to nasopharyngitis. The relation between nasopharyngitis and blood adrenocortical hormone was studied next

Urinary 17 KS and 17-OHCS are usually determined for an abnormal function test and *both methods require storage of whole day* urine. It is necessary to observe blood steroids to study changes in excretion of adrenal hormone immediately after stimulation of the nasopharynx. Plasma 11-OHCS (11 Hydroxy corticosteroids) was chosen for the purpose

Hydrocortisone and corticosterone the main adrenocortical hormones in blood which emit fluorescence on reacting with sulfuric acid were determined by a fluorometer. It was Sweat (1954) that advocated the first determination of blood steroids by a fluorometer. Sweat's method was gradually improved and De Moor (1961) established a highly reliable *method.*

Determination Method

Ten ml of methylene chlorid were added to 2 ml of plasma, shaken for 30 seconds by hand and centrifuged at 3,000rpm for 7 minutes. One 1 of 1/10 N NaOH was added to the methylene chloride layer

Table 31 Results.

Case	Name	Age	Sex	Nasopharynx		Plasma 11-OHCS (γ/dl)		
				Pain	Bleeding	Before	After	Change
1	T.H.	42	F	+	−	16.7	19.2	15%
2	H.H.	23	M	+	−	20.2	20.2	0
3	M.G.	20	F	++	−	19.0	28.5	50
4	Y.K.	29	F	+	−	34.6	23.1	−33
5	K.S.	27	F	+	−	25.8	22.8	−12
6	K.T.	28	M	++	±	14.2	20.2	41
7	S.W.	28	M	++	+	15.3	21.4	40
8	W.T.	33	F	++	+	11.5	18.3	59
9	Y.S.	19	M	++	+	13.0	20.4	57
10	T.O.	58	F	++	++	10.0	14.0	40
11	Y.H.	20	F	+	−	20.0	23.5	18
12	K.Y.	19	M	+	−	15.0	16.7	11
13	Y.S.	16	F	+	±	10.4	13.5	30
14	E.K.	20	F	++	+	13.0	18.0	39
15	Y.T.	58	F	+++	+++	6.1	19.5	220
16	I.S.	29	M	+	±	17.5	17.5	0
17	Y.T.	28	M	++	+	19.4	29.0	50
18	T.W.	20	F	++	+	30.8	28.9	−6
19	N.K.	58	M	++	+	13.0	21.0	62
20	K.T.	32	M	+	−	24.0	12.0	−50
21	M.I.	26	M	±	−	19.7	19.7	0
22	H.A.	43	F	++	++	15.0	27.5	83
23	M.S.	46	F	+	+	18.0	22.0	22
24	T.Y.	51	M	+	−	18.3	22.1	21
25	K.O.	26	F	+	−	22.1	29.8	35
26	N.M.	62	F	++	+	23.4	30.0	28
27	M.S.	53	F	+	−	27.3	30.0	9
28	O.O.	18	M	+	−	32.5	27.5	−15
29	M.Y.	52	M	++	+++	18.8	43.8	133
30	T.T.	4	M	++	−	25.5	40.0	57
31	H.H.	41	F	+	−	16.4	20.0	22
32	Y.N.	33	F	++	−	14.6	14.6	0
33	H.M.	41	M	++	−	33.3	12.5	−63
34	J.M.	33	F	++	++	7.1	10.8	52
35	A.K.	31	M	±	+	13.4	12.5	−7
36	H.M.	12	F	++	+	20.0	5.0	−75
37	T.F.	49	F	+	±	11.0	11.0	0
38	Y.T.	58	F	++	++	15.0	22.5	50
39	M.N.	38	M	++	+	27.5	33.5	22
40	H.S.	16	F	+	−	20.7	10.3	−50
41	K.K.	40	F	+	−	32.5	37.5	15
42	K.A.	38	M	+	−	31.4	33.0	5
43	K.H.	46	M	+	+	33.3	29.7	−11
44	Y.N.	8	F	++	++	18.6	30.0	60
45	T.W.	28	F	+	−	21.9	26.0	19
46	K.O.	38	M	+	+	18.3	22.5	23
47	T.O.	40	F	+	+	18.3	18.3	0
48	M.M.	37	F	++	++	14.8	21.3	44
49	M.I.	26	M	=	−	19.7	19.7	0
50	M.Y.	32	F	+	++	22.2	38.8	75
51	H.N.	16	M	+	+	16.0	23.0	40
52	Y.K.	30	F	+	−	22.5	27.3	22
53	M.K.	32	F	+++	+	16.7	22.9	37

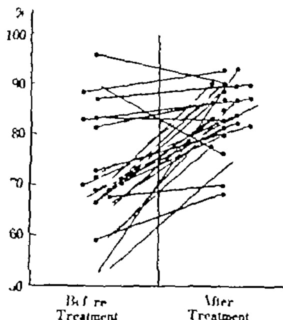


Fig 39.

serious turn because of a cold in spite of continuation of the treatment, ELT also moved backwards. Therefore there seemed to be no habituation phenomenon)

Typical ELT curves before and after the treatment of the nasopharynx were shown in Table 30 and Fig 38 In these cases ELT after the treatment became significantly longer compared to that before the treatment Those cases whose ELT was prolonged by the nasopharyngeal treatment has short ELT in other words they had acute or subacute nasopharyngitis. In chronic patients ELT was shortened or was not changed by the treatment Fig 39 showed ELT values 15 minutes after stimulation of nasopharynx in chronic patients. It was observed that there eas a tendency for ELT to remain at a constant value during the nasopharyngeal treatment

2) *Alteration of Plasma 11-OHCS*

It is a fact that rheumatism and allergy can be healed or improved very successfully only by local treatment of the nasopharynx Why has such an effect of nasopharyngeal treatment been elucidated yet? As mentioned before inflammatory foci always exist in the nasopharynx and this inflammation becomes severe in case of rheumatism or allergy Treatment of this inflammation runs parallel to treatment of these original diseases. In rheumatism for example, nasopharyngitis has the necessary and sufficient conditions to act as a source of focal infection, and also in the incipient stage of nasal allergy or asthma an abnormal feeling in the nasopharynx appears first as a premonitory symptom. And so it is most important to treat nasopharyngitis, which is one of the sources of these diseases, and to keep it from participating in their attack. It is very important to study their relation further for investigation of a mechanism of inflammation and allergy

To investigate the mechanism of causal relation between nasopharyngitis and these diseases, the relationships between nasopharyngitis and ELT and between nasopharyngitis and the autonomic nervous system have been studied and reported It is known that ELT is accerlated in proportion to aggravation of inflammation in case of rheumatism and a kind of abnormality in a mechanism of autonomic nerve has an important relation to acceleration or disappearance of inflammation.

It is also clear that an accelerated condition of ELT and an abnormal condition of the autonomic nerve and parallel to nasopharyngitis. The relation between nasopharyngitis and blood adrenocortical hormone was studied next

Urinary 17 KS and 17-OHCS are usually determined for an abnormal function test and both methods require storage of whole day urine It is necessary to observe blood steroids to study changes in excretion of adrenal hormone immediately after stimulation of the nasopharynx. Plasma 11-OHCS (11 Hydroxycorticosteroids) was chosen for the purpose

Hydrocortisone and corticosterone the main adrenocortical hormones in blood which emit fluorescence on reacting with sulfuric acid were determined by a fluorometer It was SWEAT (1954) that advocated the first determination of blood steroids by a fluorometer SWEAT's method was gradually improved and De Moor (1961) established a highly reliable method

Determination Method

Ten ml of methylene chlorid were added to 2 ml of plasma, shaken for 20 seconds by hand and centrifuged at 3 000rpm for 7 minutes. One ml of 1/10 N NaOH was added to the methylene chlorid layer

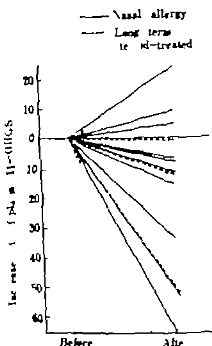


Fig. 43. Nasal allergy and long term steroid-treated cases (18 cases)

after the stimulation were calculated taking that before the nasopharyngeal stimulation as 0. The same data shown in Fig. 40 were used. Even in this figure change rates increased significantly after the stimulation in some subjects, while decreasing in others. Remarkable distinctions were found, however, by applying these increasing and decreasing cases to cases of nasopharyngitis. These 53 subjects were divided into 2 groups, namely 35 subjects suffering simply from nasopharyngitis (Fig. 42) and 18 subjects with nasal allergy or who had been taking steroids for a long term (Fig. 43) and a remarkable difference was observed by comparing these 2 groups.

In subjects with only nasopharyngitis, plasma 11-OHCS increased in all cases after stimulation of the nasopharynx and reached +133% or +220% in some subjects, while in subjects taking steroids or with nasal allergy plasma 11-OHCS after nasopharyngeal stimulation did not change, or rather decreased. Plasma 11-OHCS increased more significantly in the subjects with more severe inflammation in the nasopharynx, as in Fig. 42. However in the subjects with nasal allergy or who had been taking steroids for a long term plasma 11-OHCS decreased after stimulation of the nasopharynx in spite of their having severe nasopharyngitis. This fact seemed to show that the mechanism of steroid excretion, the mechanism of ACTH excretion or that of CRF excretion from the hypothalamus was weakened.

As plasma 11-OHCS was altered easily (De Moor, 1960, 1962; Bliss, 1953) it was necessary to observe changes of plasma 11-OHCS for 15 minutes without any nasopharyngeal stimulation as a control. Table 32 and Fig. 44 were prepared for this reason. In the subjects shown in Fig. 41, 42 and 43 the nasopharynx was stimulated between 2 blood-drawings, while in the subjects shown in Table 32 and Fig. 44 blood was taken after 15 minutes without nasopharyngeal stimulation. Values of 11-OHCS varied also in Fig. 44 but they changed little during the 15 minutes. The mean and standard deviation of 11-OHCS after 15 minutes was $-8 \pm 9.4\%$ which showed a slight decrease. Therefore it could be said that 11-OHCS hardly changed or rather decreased during the 15 minutes when the nasopharynx was not

Table 32. Plasma 11-OHCS concentration (γ/dl) without stimulation

Case	Name	Age	Sex	Before	After	Differ	Rate ( )
1	A.Y.	19	M	21.1	21.2	−1.9	− 8
2	Y.M.	23	M	24.1	22.2	−1.9	− 8
3	N.M.	20	F	19.2	19.2	0	0
4	T.O.	22	M	21.0	19.5	−1.5	− 7
5	A.A.	24	F	10.9	7.8	−3.1	−28
6	M.M.	[illegible]0	M	6.1	6.1	0	0
Mean				17.4	16.0	−1.4	− 8 ± 9.4

Measured between 3-4 p.m.

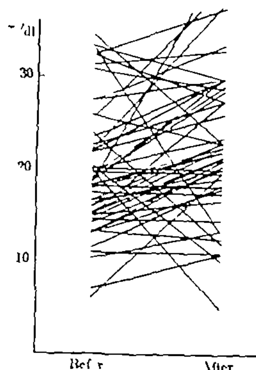


Fig 40. Plasma 11-OHCS after stimulation of the nasopharynx (53 cases)

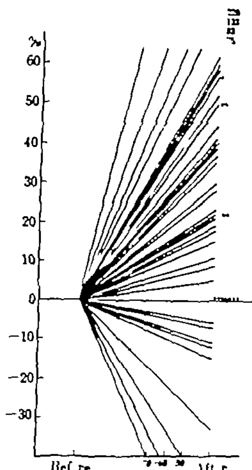


Fig. 41 Plasma 11-OHCS after stimulation of nasophary (53 cases)

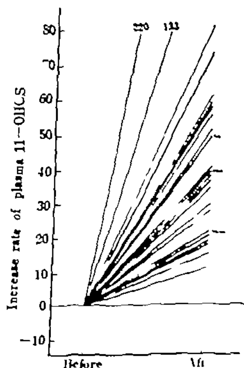


Fig 42. Nasopharyngitis simplex (53 cases)

the bottom layer which was shaken for 15 seconds, while the upper NaOH layer was removed completely The methylene chloride layer was washed one more time with 1/10 N NaOH. The same procedure was conducted on both blank and standard reagents.

Five ml of a reagent (70° sulfuric acid in ethanol) were added to the extract thus obtained, shaken for 30 minutes by hand and the upper methylene chloride layer was removed. The bottom sulfuric acid ethanol layer was tested by a fluorometer

Fluorescence was determined exactly 15 minutes *after adding the reagent*

The author determined plasma 11-OHCS by the above method and studied whether 11 OHCS was changed by the nasopharyngeal stimulation (YAMADA, 1972) As plasma 11 OHCS changes easily the author made every possible effort to catch changes caused by the nasopharyngeal stimulation if there were any By actually measuring plasma 11-OHCS of 53 subjects before and 15 minutes after the stimulation of nasopharynx the author got the data shown in Table 31 and Fig 40 which were so variable that they could not be controlled Plasma 11-OHCS before and after the stimulation of nasopharynx changed in some subjects, did not change in others, increased in some subjects and decreased in others. So as shown in Fig 41 the change rates of plasma 11 OHCS

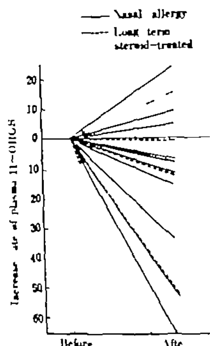


Fig. 43. Nasal allergy and long term steroid-treated cases (18 cases).

after the stimulation were calculated taking that before the nasopharyngeal stimulation as 0. The same data shown in Fig 40 were used. Even in this figure change rates increased significantly after the stimulation in some subjects, while decreasing in others. Remarkable distinctions were found, however by applying these increasing and decreasing cases to cases of nasopharyngitis. These 53 subjects were divided into 2 groups, namely 35 subjects suffering simply from nasopharyngitis (Fig 42) and 18 subjects with nasal allergy or who had been taking steroids for a long term (Fig 43) and a remarkable difference was observed by comparing these 2 groups.

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As plasma 11-OHCS was altered easily (De Moor, 1960, 1962 Bliss, 1953) it was necessary to observe changes of plasma 11-OHCS for 15 minutes without any nasopharyngeal stimulation as a control. Table 32 and Fig 44 were prepared for this reason. In the subjects shwon in Fig 41 42 and 43 the nasopharynx was stimulated between 2 blood-drawings, while in the subjects shown in Table 32 and Fig 44 blood was taken after 15 minutes without nasopharyngeal stimulation. Values of 11-OHCS varied also in Fig 44 but they chenged little during the 15 minutes. The mean and standard deviation of 11-OHCS after 15 minutes was -8 ± 9.4 %, which showed a slight decrease. Therefore it could be said that 11-OHCS hardly changed or rather decreased during the 15 minutes when the nasopharynx was not

Table 32 Plasma 11-OHCS concentration (γ/dl) without stimulation

Case	Name	Age	Sex	Before	After	Differ	Rate (%)
1	K.Y	19	M	23.1	21.2	−1.9	− 8
2	Y M.	23	M	24 1	22.2	−1.9	− 8
3	N M.	20	F	19.2	19.2	0	0
4	T.O.	22	M	21.0	19.5	−1.5	− 7
5	K S	24	F	10.9	7.8	−3.1	−28
6	M M.	40	M	6.1	6.1	0	0
Mean				17 4	16.0	−1 4	− 8 ± 9.4

Measured between 3–4 p.m.

stimulated.

In simple nasopharyngitis, 11-OHCS increased immediately after stimulating the nasopharynx as shown in Fig 42. What was the the extent of this increase?

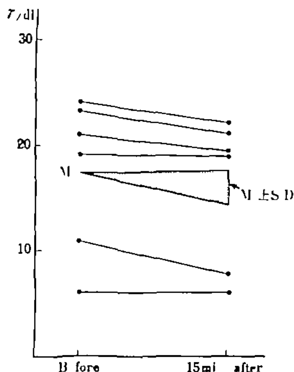


Fig 44. Plasma 11-OHCS concentration without stimulation.

In Fig 45 the nasopharyngitis was roughly divided into 3 groups, namely slight, moderate and severe, and increasing rates of 11-OHCS in each group were shown. It was found that increasing rates of 11 OHCS were higher in marked nasopharyngitis. This increase might come from the stress, as abrasive pain was severer in marked nasopharyngitis than in slight cases. However YAMADA (1970 1972) conducted various control experiments and ruled against this possibility In the subjects with nasal allergy (dotted line) and those who had used steroids for a long term (broken line) 11 OHCS decreased after the stimulation, showing no connection with the condition of nasopharyngitis, which was probably due to lowering of adrenocortical and pituitary functions. This phenomenon seems to be interesting material for explaining the mechanism of getting allergy

Cessation of Long-term Steroid Treatment after Treating Nasopharyngitis

In the preceding chapter it was mentioned that blood 11 OHCS decreased immediately after stimulating the nasopharynx in those subjects who had been taking steroids for a long

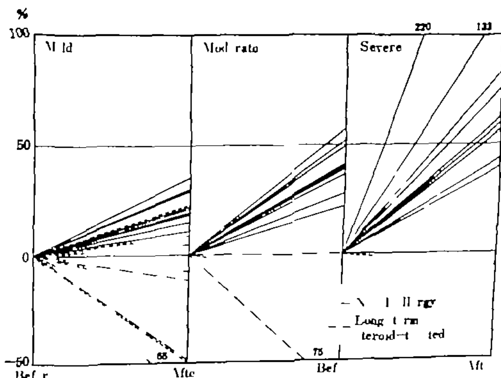


Fig 45. Degree of inflammation of nasopharynx and increase rate of plasma 11-OHCS.

term. This was observed typically in the patients with the so-called moon faces suffering from the side effects of steroids and having difficulties in withdrawing from steroids. When nasopharyngeal treatment was conducted on the patients with rheumatism, arthralgia and swelling of the joints disappeared, and RA and ASLO were improved as if steroids were administered. Therefore nasopharyngeal treatment was tried on the above-mentioned patients suffering from the side effects of steroids for the purpose of aiding their withdrawal from the steroids. It was found that various symptoms of rheumatism were improved and no more rheumatic fits were observed after stopping steroid administration and switching to nasopharyngeal treatment. Toxic symptoms of steroids were improved gradually and 11-OHCS after the stimulation, which was (−) before the treatment, increased gradually and was restored to its normal value.

Fig 46 shows patients with rheumatism suffering from the side effects of steroids, for whom steroid administration was stopped and nasopharyngeal treatment was given instead.

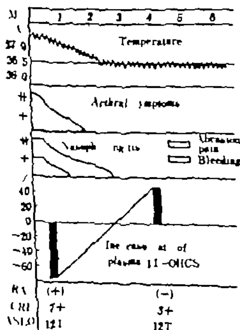


Fig. 46. Long term steroid-treated Case. H.M. 19 y, F. Rheumatoid arthritis.

Slight fever and joint symptoms had almost disappeared 2 months after starting the treatment. 11-OHCS measured at the beginning of the treatment was −60% however increased to +40% after 4 months. Severe abrasive pain and bleeding after abrasion were observed at the beginning, but the bleeding stopped after about 1 month and abrasive pain disappeared after 3 months. As could be seen in these patients, the following facts were found when steroids were taken for a long term.

1. Excretion of 11-OHCS after the nasopharyngeal stimulation was decreased.
2. After stopping nasopharyngeal treatment and steroid administration, plasma 11-OHCS after the nasopharyngeal stimulation gradually came near its normal value.

It is generally said that an operation during steroid administration is dangerous as it may cause a shock and when steroid administration is stopped suddenly life may be in danger. Considering this fact together with the phenomenon that excretion of steroids decreased immediately after stimulation of the nasopharynx, it seems more probable that excretion of steroids decreases because of stimulation by stress rather than that steroids are not excreted sufficiently when a living body is stressed. It is important to determine whether this decrease of plasma 11-OHCS after the stimulation occurs simply as a related phenomenon or whether the decrease of steroids itself is directly related to the shock. However it is not known which is the case.

When nasopharyngeal treatment is conducted on the patients with difficulty in withdrawing from steroids, steroids are withdrawn relatively easily in many cases (In some cases it is improved on the day when the treatment is started.) The mechanism, however is not clear yet. Since excretion of steroids decreased after nasopharyngeal stimulation.

1. The mechanism of attacks, which were suppressed by nasopharyngeal treatment, might not be related to steroids.

2. Since observations were conducted for 15 minutes after stimulation of the nasopharynx in this study the phase, where excretion of steroids in blood was increased, might be seen by observing for a longer term.

These problems will be solved by continuing

stimulated

In simple nasopharyngitis 11-OHCS increased immediately after stimulating the nasopharynx as shown in Fig 42 What was the the extent of this increase?

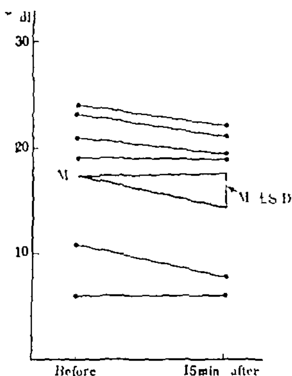


Fig. 44. Plasma 11-OHCS concentration without stimulation.

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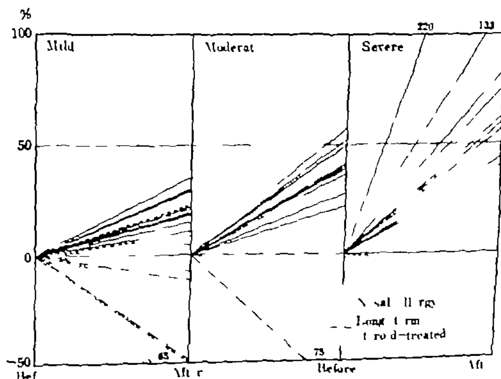


Fig 45. Degree of inflammation of nasopharynx and increase rate of plasma 11-OHCS.

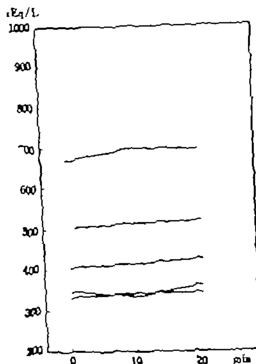


Fig. 47 Plasma FFA concentration without stimulation.

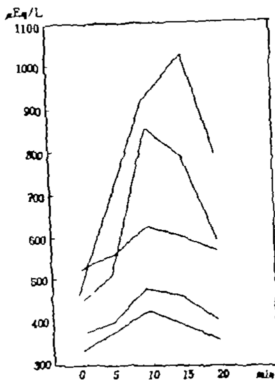


Fig. 48. Change of plasma FFA after nasopharynx stimulation.

period and external stimulations were a oides as much as possible.

Serum was kept in refrigerator immediately after its separation. Determination of FFA was conducted 3 to 4 hours afte blood drawing.

Spontaneous Changes f FF 1 in Plasma

I was mentioned before that FFA in blood is altered by arious factors. It is said that FFA n blood increases gradually w th hunger as blood ugar decreases. Spontaneous changes of plasma FFA were tested on 3 subjects and t was found that FFA changed little between 0 and 20 minutes as show in Fig 47 In other words it was confirmed that FI A did ot hange during 20 minutes, which was necessary for th next step, unless special treatments were gi en.

Ulteration f Plasma FF 1 with Time after Naso-pharyngeal Stimulation

Nasopharyngeal irritation has as much ffect on the tonomic nerv as stress, and it is quite possible that plasma FFA changes by naso-pharyngeal stimulation.

Therefore how plasma FFA changed with time after nasopharyngeal stimulation was studied.

Blood was taken 5 times, namely before stimulation, 5 minutes, 10 minutes, 15 minutes and 20 min tes after stimulation and FFA in the plasma specimens from 5 subjects was deter mined (Fig 48) As shown in Fig 48, it wa found that plasma FFA increased significantly after nasopharyngeal stimulation. A peak wa reached 10 minutes after nasopharyngeal stimu lation in 4 subjects, 15 minutes after stimulatio in 1 subject, and then plasma FFA decreased gradually to the value before stimulation.

The average increasing rate after 10 minute was 54±38.2% in 5 subjects and after 2 minutes it was 23 These values were quit different from the increasing rates of spontane ous changes in 10 and 20 minutes, which wer 2.2±2.3 and 4 4±0.8% respectively Thi fact suggested that plasma FFA responded t nasopharyngeal stimulation sensitively through adreno-sympathetic control.

Increasing Rates f Plasma FFA in the Patient

this study further but it is certain that nasopharyngeal treatment improves most rheumatisms and allergies as administered steroids do

By what kind of mechanism does plasma 11 OHCS decrease immediately after stimulating the nasopharynx of the patients who have been taking too much steroids?

ACTH from the pituitary is necessary for excretion of steroids in blood and for this stimulation CRF (Corticotropin Releasing Factor) from the hypothalamus is necessary It is not known how the nasopharyngeal stimulation affects this pathway However it can be imagined that the stimulation of the nasopharynx affects directly the hypothalamus. For example, in disfunction of the thyroid gland nasopharyngeal treatment normalized basal metabolism effectively in some cases and a similar fact was also observed in the liver function. From this finding it is presumed that stimulation or treatment of the nasopharynx stimulates the hypothalamus or corrects disfunction of the hypothalamus and normalizes abnormal conditions of various organs via the hypothalamus. It is also presumed that stimulation of the nasopharynx or treatment of its inflammation affects centers of the autonomic nerve system such as the hypothalamus

Further experiments are needed to show whether decrease in excretion of 11 OHCS by stimulation of the nasopharynx results from atrophy of the adrenal cortex or from temporary malfunction Judging from the fact that 11 OHCS which was decreased after the stimulation easily recovered after nasopharyngeal treatment, it can be thought that decrease in the function of the adrenal cortex was only temporary at least in our subjects It is often observed by autopsy that patients who used to take too much steroids, have an adrenal cortex as thin as a sheet of paper Can such an atrophied adrenal cortex be treated so easily by discontinuing steroids and stimulating the nasopharynx, or is nasopharyngeal treatment not effective in such patients? These questions are left to be answered

3) **Alteration of γ globulin** (Will be treated later)

4) **Alteration of Free Fatty Acids in Plasma**

Free fatty acids (FFA) in plasma are altered by various factors. For example glucose prevents their emigration while growth hormone ACTH adrenalin and noradrenalin accelerate their emigration It is known that FFA in plasma quickly changes under adreno-sympathetic control, and their change can be prevented by administering autonomic nerve blocking agents beforehand Therefore by observing the change of FFA in plasma caused by nasopharyngeal stimulation we can surmise how change of adreno-sympathetic control takes place.

Procedure for Determination (Improved DUNCAN s Colorimetric Method)

0 4 ml of serum was pipetted into a centrifuge tube with a stopper and 6.0 ml of chloroform and 2 0 ml of copper nitrate reagent were added. The mixture was shaken vigorously and centrifuged at 2,500 rpm for 5 minutes. The supernatant was removed completely by an aspirator 3 0 ml of the remaining chloroform layer was transfered to a test tube with a stopper 1 0 ml of a color reagent was added mixed well and let stand for 15 minutes at room temperature. The optical density of the solution was measured with a photoelectric colorimeter against a blank. The optical density of a standard solution was obtained by processing 1 mEq/l of palmitic acid in the same way FFA in blood was calculated according to the following equation

$$\frac{E(A)}{E(S)} = \text{mEq FFA}/l$$

F(A) = Optical density of the sample
E(S) = Optical density of the standard solution

Though the amount of FFA in plasma is very small compared to other lipids, it changes rapidly in plasma. As FFA in plasma is apt to be affected by various metabolic systems, the conditions of determination have to be kept constant and other effects have to be diminished as much as possible.

Patients fasted after having supper the night before and visited the hospital at 9 a m After lying quietly on a bed for about 30 minutes, blood was taken from an elbow vein and the nasopharynx was stimulated immediately after The patients lay quietly on a bed during this

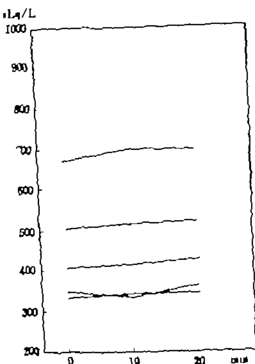


Fig. 47 Plasma FFA concentration without stimulation.

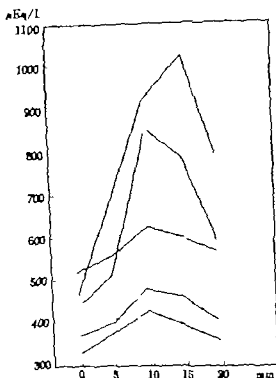


Fig. 48. Change of plasma FFA after nasopharynx stimulation.

period and external stimulations were voided as much as possible.

Serum was kept in a refrigerator immediately after its separation. Determination of FFA was conducted 3 to 4 hours aft blood drawing.

Spontaneous Changes of FFA in Plasma

It was mentioned before that FFA in blood is altered by various factors. It is said that FFA in blood increases gradually with hunger as blood sugar decreases. Spontaneous changes of plasma FFA were tested on 5 subjects and it was found that FFA changed little between 0 and 20 minutes as shown in Fig 47. In other words it was confirmed that FFA did not change during 20 minutes, which was necessary for the next step, unless special treatments were given.

Alteration of Plasma FFA with Time after Nasopharyngeal Stimulation

Nasopharyngeal irritation has as much effect on the autonomic nerv as trem, and it is quite possible that plasma FFA changes by nasopharyngeal stimulation.

Therefore how plasma FFA changed with time after nasopharyngeal stimulation was studied.

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The average increasing rate after 10 minutes was 34 ± 38.2* in 3 subjects and after 20 minutes it was .3. These values were quite different from the increasing rates of spontaneous changes in 10 and 20 minutes, which were 2.2 ± 2.3 and 4.4 ± 0.8 respectively. This fact suggested that plasma FFA responded to nasopharyngeal stimulation sensitively through adreno-sympathetic control.

Increasing Rates of Plasma FFA in the Patients

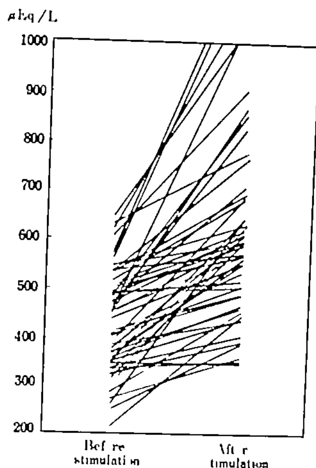


Fig. 49 Change of plasma FFA before and after stimulation (t first visit)

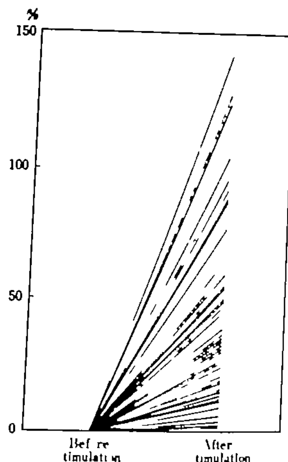


Fig. 50. Increase rate of plasma FFA after stimulation of the nasopharynx (At first int)

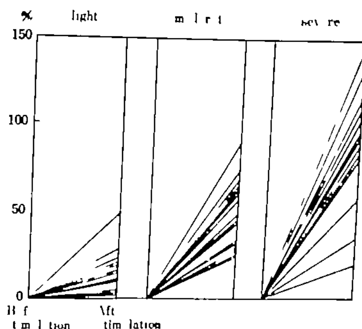


Fig 51 Degree of inflammation of the nasopharynx and increase rate of plasma FFA.

with Nasopharyngitis

As mentioned previously plasma FFA hardly changed between 10 and 20 minutes when the nasopharynx was not stimulated.

Figs. 49 and 50 show plasma FFA determined immediately before and 10 minutes after nasopharyngeal stimulation at the first medical examination of 50 patients diagnosed as having nasopharyngitis. As plasma FFA changes by the effect of various metabolic systems, plasma FFA of the same subject varies when the conditions of determination change. However the change was very slight as shown in Fig 47 when taking time difference (10 minutes) of 2 determinations (before and after stimulation) (Compare Figs. 47 and 48.) In nasopharyngeal stimulation, it could be observed that plasma FFA increased in 48 out of 50 subjects as shown in Figs. 48, 49 and 50. Its increasing rate extended over wide range (1–142%) and no change was observed in 2 subjects.

Relation between the degree of nasopharyngeal inflammation and plasma FFA was studied next. It was found that there was a correlation between the degree of inflammation and the increasing rate of plasma FFA. This was similar to the case of 11-OHCS reported in the preceding chapter

Increasing rate of plasma FFA in the patients with slight nasopharyngitis was $15\pm13.2\%$, 48 ± 18.7 in the patients with moderate nasopharyngitis and 88 ± 32.9 in those with marked nasopharyngitis (Fig. 51)

Improvement of Nasopharyngitis and Increasing Rate of Plasma FFA

It was studied how increasing rates of plasma FFA changed according to the treatment of nasopharyngitis.

Among 50 cases, changes were observed in 26 cases. The treatment period was 2 weeks in the shortest case, 1 to 2 months in most cases and some patients were treated for over a year. With a few exceptions where treatment was discontinued before complete recovery, satisfactory effect was observed in 24 out of 26

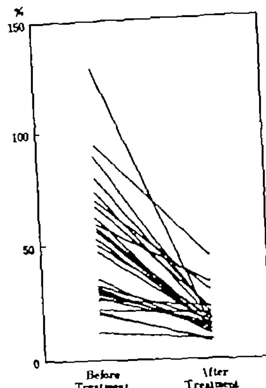


Fig. 52. Increase rate of plasma FFA after improvement of nasopharyngitis.

patients. When increasing rates of plasma FFA were determined at this stage, the values decreased in all cases compared to those at the first medical examination and were between 10 and 30% in 20 out of 26 patients (76%) as shown in Fig 52. From these results it can be said that increasing rates of plasma FFA show not only the degree of nasopharyngitis but also the course of recovery of the inflammation and the reaction of the autonomic nerve against stress, the stimulation of the nasopharynx. In other words, an abnormal reaction, which is observed in sudden increase of plasma FFA, is controlled by nasopharyngeal treatment and this is supposed to show that nasopharyngeal treatment plays a roel as a kind of homeostasis to correct an overreaction of the body

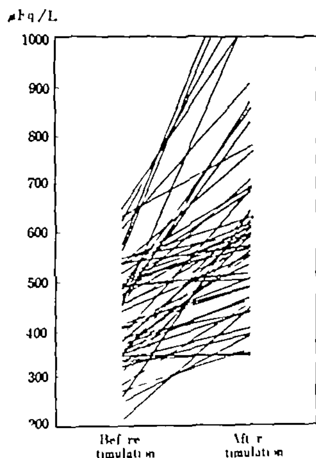


Fig 49 Change of plasma FFA before and after timulation (at first sit)

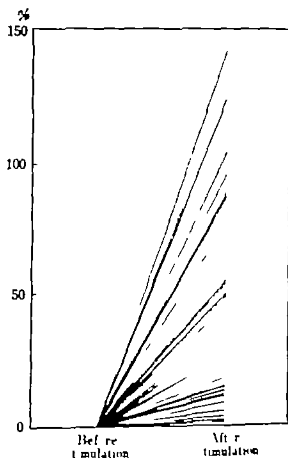


Fig 50. Increase rate of plasma FFA after stimulation of the nasopharynx (At first sit)

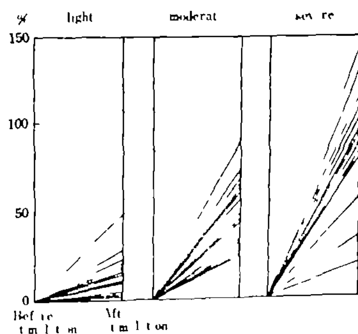


Fig 51 Degree of inflammation of the naso- phary and incre se rat of plasma FFA

Part II

Clinical Aspects of Nasopharyngitis

Nasopharyngitis is a latent inflammatory focus which exists in a large number of people. The presence of the inflammatory focus can be confirmed by examining smears obtained from the nasopharyngeal mucosa and its course can be accurately detected. The local treatment of nasopharyngitis shows interesting clinical phenomena along with alleviation of the inflammation. In the following pages the author will discuss the clinical observations in due order

1 Significance of the Presence of Latent Inflammatory Focus in Nasopharyngitis

The presence of a latent inflammatory focus in the nasopharynx of majority of people is meaningful in various ways. Among these, the focal infection is an important characteristic of nasopharyngitis. Focal infection, like tonsillitis in rheumatism, had been assumed by many investigators as the basis of the hypothesis that its focus might act as the origin of various diseases. Nevertheless, not many inflammatory foci were found to become source of infection, just as tonsillitis was not always detected in rheumatic patients. This is true also regarding the theory of prolonged sensitization of OKABAYASHI.

OKABAYASHI (1963) observed prolonged sensitization after repeated forced infection in animals, which finally developed kind of autoimmune disease and succeeded in producing autoimmune diseases like SLE or rheumatism. The results of the experiments were considered transferrable to human data, but clinicians failed to confirm the presence of chronic focal infection except in few cases of tonsillitis. Thus the assumption of a chronic focal infection could not demonstrate the relationship between the focus and the onset of SLE or rheumatism, as successfully observed in animal experiments. We consider that autoimmune disease including the so-called collagen disease (in which autoantibody is not always detected) is closely related to existence of the inflammatory focus called nasopharyngitis through many clinical experiments. To demonstrate such relation is quite simple.

1. To examine the nasopharynx of the patients with autoimmune disease or collagen disease and confirm the presence of inflammation.
2. If nasopharyngitis is confirmed, employ a simple medication (1% $ZnCl_2$) and apply it with a cotton applicator into the nasopharynx and observe the response to the manifested diseases.
3. The local treatment as such is equal to artificial sounding of the infectious focus. In this we can observe the effect of the nasopharyngeal treatment in parallel to the clinical course of the manifested diseases.

1) Rheumatism

In the following chapters we will discuss the possibility of focal inflammation provoking autoimmune diseases such as rheumatism. Rheumatism may be classified into chronic rheumatoid arthritis and rheumatic fever and both of these are closely related to nasopharyngitis. Clinically rheumatism is always associated with intense nasopharyngitis and the local treatment can bring its cure or improvement.

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1 Significance of the Presence of Latent Inflammatory Focus in Nasopharyngitis

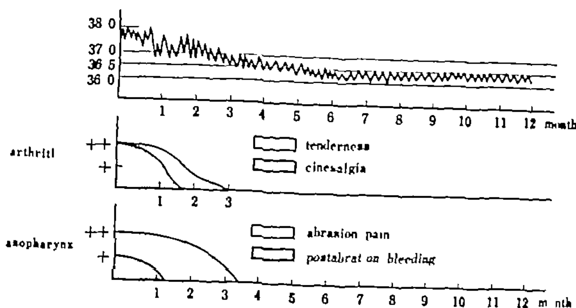
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1) Rh umatism

In the following chapters we will discuss the possibility of focal inflammation provoking autoimmune diseases such as rheumatism. Rheumatism may be classified into chronic rheumatoid arthritis and rheumatic fever and both of these are closely related to nasopharyngitis. Clinically rheumatism is always associated with intense nasopharyngitis and the local treatment can bring is cure or improvement.



Clinical courses of nasopharyngeal treatment.

Date	ASLO	CRP	RA	Micro-organism	Contraction time of pulse wave	ELT	BSR
t the first exam.	525	3+	–	Str irid (++) diplo (++)			91/h
after months	625	4+	–	Str virid (++)	200 sec	125 min.	105
after 3 months	500	3+	–	Str virid (++)	130	150	
after 4 months	333	2+	–	Str irid (+)			45
after 6 months	250	2+	–	Str virid (+) diplo (+)	90	115	
after 12 months	166	–	–	Staphylo epid (++)			

Fig 53. Case No. 1 U T 32 Y o. F

Case No 1 (Fig 53)

U T A 32 year old female with rheumatic fever

Chief complaints A pain in the nasopharynx and in the knee joint

History No specific diseases were recorded in her family

In March 1965 she had pain in the throat with fever of 40 C which continued for 10 days. Since then she was susceptible to cold and often attacked by fever of 40 C with a prodromal symptom of the pain in the throat She visited an internist but she did not get well In February 1967 she had a similar attack and complained of pa n in the knee joint. She suffered from unlocalized pain in other places of the body also.

In March 1967 she was diagnosed as ha ng rheumatic fever by one of our colleagues. She had a normal temperature of about 37 C

Labor tory finding

ECG within normal range Chest X-ray was normal.

Blood sedimentation, 30–45mm, 1 00–91mm, 2 00–140mm.

Serum ASL-O values, 625 T U

CRP ### RA (+)

Diagnosis After close examination at the medical department of this university rheumatic fever was indicated.

Nasopharynx. A marked abrasion pain (++) and abrasion hemorrhage (+) were observed. The nasopharyngeal abrasion preparation revealed a markedly ntense exfoliation and transformation of ciliated epithelial cells and a large number of treptococci iridans and Gram negati e diplococci were identified. Sl ght hypertrophy of th palatin tonsil was observed, but no inflan mation existed

Clinical course of nasopharyngitis. Clinical course after in tial examination is show Fig 53. All medications were discontinued except the local treat ent of nasopharyngitis. Th local inflammation n the nasopharyn wa *intense and resisted* the treatment. The post bras e *hemorrhage continued for bout 40* days. (Usually bleeding terminates in 10–14 days.) Abrasion pain finally disappeared after

three months of treatment. (Simultaneous disappearance of inflammation was obtained.) (Generally abrasion pain disappears in 1 3 weeks in parallel to alleviation of inflammation.)

The patient fever dropped to normal state (Below 37.5°C constantly.) It took long time to completely cure the disease (6 months of daily treatment) Also it took about one year until the serum ASLO alues returned to normal. (The last column of diagram.) The rise and fall of bacterial flora is also shown in the diagram. Non toxic staph. epidermis appeared only after normalization of serum alues. The diagram also indicates prolonged contraction period of pulse w of the fingertip (The Basic Study of Nasopharyngitis). Measurement of the pulse w was intended to examine how rheumatism affects the autonomic nerves of the peripheral site, but this may be observed ir respecti of the presence of rheumatism. As above case of rheumatic fever was studied. From that you can see that complete cur requires local treatment for long period. The case which lead to complete heal has few relapses, if any will be easily cured by the local treatment.

Case No. 2 (Fig. 54)

ILT A 22 year old male with chronic rheumatic arthritis.

Chief complaint Pain in bilateral knee joints.

History The pain attacked his right knee joint after work. It reached both knee joints and the gait was disturbed. H isited an orthopedic clinic and was diagnosed as ha ing chronic arthritis. In spite of arious medica ions he did not get well. In winter besides the knee joints, he felt pain and swelling in the achilles tendon. He then felt pain in the right shoulder or in both ankles. Various treatments were tried but in vain.

Clinical findings ECG remained normal, erythrocyte sedimentation

30'–5mm.

1 10mm.

2 –18mm.

Serum ASLO 166 T U CRP ++ RA (−)

Temperature At time of admission to the hospital, the fever ranged around 37°C.

Diagnosis After intensive examination by an orthopedic surgeon, the patient was diagnosed as having chronic rheumatoid arthritis.

Nasopharyngitis Routine ORL examination failed to detect abnormality in the nasopharynx but application of a cotton pplicator dipped in 1% $ZnCl_2$ at the dorsal surface of soft palate caused severe abrasion pain and bleeding which ran dow through the wall of the nasopharynx. I tense erosion and marked inflammation were observed at the back of the soft palate. The smear preparation indicated a large amount of exfoliated and transformed ciliated epithelial cells and emigration of leucytes. A large number of streptococci viridans and staphylococci aureus were observed. It must be noted that the patient had no subjective symptoms in the nasopharynx and routine ORL examination failed to detect abnormality but an intense, severe inflammation was present. Such phenomenon is general pictur of nasopharyngitis and it is the reason why the nasopharyngitis had been missed by the medical profession.

Clinical course Patient response to the treatment is shown in Fig. 54.

Postabrasi hemorrhage as esult of the nasopharyngeal treatment was persistent for about one month and the abrasion pain continued for two months. A slight fever was observed for the first one month but he returned to normal in three months. Since commencement of the treatment all other medications and treatments had been discontinued. In response to the treatment, the inflammation was reduced and at the same time rheumatic symptoms gradually disappeared. The spontaneous pain in the joints disappeared in one to fi months, and the kinesalgia and tenderness were improved in three months. The patient felt slight stiffness in the ankle joint or achilles tendon early in the morning and after exercise. In the fourth month he caught cold again and the pain attacked both knees. Abrasion pain and post abrasi bleeding were observed. The smear preparation indicated exacerbation of the inflammation. After two to three days of the

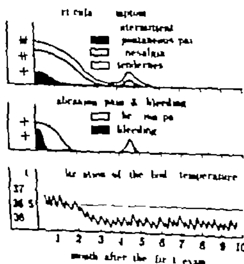


Fig. 54. Case No. 2) *Clinical course of typical case.* ILT 22 y. o. M.

local treatment he got well. Disappearance of the symptoms brought disappearance of the local inflammation. After continuous treatment C.R.P became negative in four months and the bacterial flora inactive (negative) The nasopharyngeal treatment with 1 $ZnCl_2$ had been continued for about one year every other day or twice weekly At the end of the year it was carried out once a week. (Since the treatment was experimental, the same method had been employed throughout the period.) No recurrence was observed in this patient after being cured

Treatment of Rheumatism as a Complication of Nasopharyngitis

As mentioned previously moderate to severe nasopharyngitis without manifest subjective symptoms has been detected in 80 % of normal persons, but a latent inflammatory focus always exists in rheumatic patients. Table 33 shows the results of the examinations in 14 randomly selected cases.

The patients with rheumatism were treated for nasopharyngitis in our ORL clinic and 15 cases of chronic arthritis and 9 cases of rheumatic fever were selected for the study All other medications were discontinued except the local treatment of nasopharyngitis with 1 $ZnCl_2$ solution and the patients response to the treatment are indicated in Table 34

Assessment of clinical results is carried out in accordance with the following criteria.

Cured No appearance of arthritic symptoms for over three years.

Table 33 Grade of inflammation of nasopharyngitis in rheumatic cases.

Cases of rheumatism	Nasopharyngitis		
	Smear preparation	Abrasion pain	Abrasion bleeding
No. 1	inflammation (+)	++	
	inflammation (+)	++	
3	inflammation ( )		
4	inflammation (+	++	+
5	inflammation (+)	++	+
6	inflammation ( )	++	
7	inflammation (+)	+++	++
8	inflammation (+)	+	
9	inflammation (+)	++	
10	inflammation (+)	+++	+
11	inflammation (+)	++	+
12	inflammation (+)	++	++
13	inflammation (+)	++	+
14	inflammation (+)	++	

Table 34 Results of the nasopharyngeal treatment in rheumatism.

1) 22 cases of chronic rheumatoid arthritis	
Cured	6 cases
Improved	7 cases
Rather improved	6 cases
Unchanged	3 cases
2) 9 cases of rheumatic fever	
Cured	6 cases
Improved	3 cases
Unchanged	0

(In formal cases for over 5 years) Disappearance of objective symptoms of arthritis and normal temperature has been maintained Improvement of serum reaction.

Improved Alleviation of arthritic symptoms as compared with those before treatment and recovery to normal activity Attainment of lowering of the body temperature Serum levels unsatisfactory

Unchanged No improvement has been attained in arthritic symptoms and other clinical findings.

Certain cases did not pass three years from commencement of the treatment Some were transferred from the improved group to the cured group

Degrees of chronic rheumatoid arthritis are classified according to the Steinbrocker classification into grades I II and III In the grade I group a considerable number of complete cures could be seen but in grades II and III good results could not be expected and especially the patients of grade III with deformed joints did not respond to the treatment Alleviation of pain was the best result we could expect in these patients.

In contrast patients belonging to grade I responded fairly well to the treatment As shown in Table 35 five out of 11 were cured Most of them maintained a normal state for a long time As shown in Table 36, favorable answers were returned to us from the patients who were cured three years ago

As shown in Table 37 we studied 9 cases of rheumatic fever Some of them showed a good response to the treatment in one month but

Table 35 Case of chronic rheumatoid arthritis.

Case No.	Age	Sex	Steinbrocker	Duration of treatment	Result
1	21	♀	I	10 months	cured
2	28	♀	I	6 months	improved
3	40	♀	I	9 months	cured
4	22	♂	I	13 months	improved
5	23	♂	I	10 months	cured
6	37	♀	I	4 months	cured
7	20	♀	I	2 months	cured
8	23	♂	I	3 months	rather improved
9	20	♀	I	3 months	improved
10	40	♀	I	3 months	improved
11	73	♂	I	4 months	rather improved
12	25	♀	I	4 months	improved
13	24	♀	II	6 months	improved
13	24	♀	II	6 months	cured
14	16	♀	II	12 months	rather improved
15	48	♀	II	3 months	unchanged
16	12	♂	II	10 months	improved
17	[illegible]	♀	II	4 months	rather improved
18	36	♀	II	2 months	improved
19	32	♀	III	15 months	unchanged
20	[illegible]	♀	III	3 months	rather improved
21	21	♀	III	6 months	rather improved
22	42	♀	III	3 months	unchanged

Table 36 Late results of the nasopharyngeal treatment in rheumatism (Answer to questionnaire from the case 3 years after the treatment).

Answer to questionnaire		No. of cases
Symptoms of rheumatism (arthralgia)	(−)	10
	occasionally (+)	4
	(+)	0
Fever	(−)	12
	occasionally (+)	2
	persistent	0
General condition	well	
	sometimes ill	6
	ill all the time	1
Nasopharyngeal condition	well	14
	ill	0
Concurrent treatment	( )	10
	occasionally	2
	continuously	2

Table 37 Case of rheumatic fever treated by the nasopharyngeal treatment.

Case No.	Age	Sex	Diagnosis	Duration of the treatment	Result
1	34	♂	rheumatic fever	8 months	cured
2	27	♀	rheumatic fever	6 months	cured
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4	15	♀	rheumatic fever	1 month	cured
5	14	♀	rheumatic fever	2 months	cured
6	30	♀	rheumatic fever	6 months	cured
7	10	♂	rheumatic fever	5 months	improved
8	8	♀	rheumatic fever	1 months	improved
9	32	♀	rheumatic fever	10 months	improved

most of them had to be treated for five to six months. In these cases, like chronic rheumatoid arthritis, the treatment was nothing but an application of 1 $ZnCl_2$ to the inflammatory site. To our regret, these patients were mild cases with normal ECG (though some had slight ECG abnormality but soon recovered after the nasopharyngeal treatment).

We observed that all cases of chronic rheumatoid arthritis and rheumatic fever exhibited

local treatment he got well. Disappearance of the symptoms brought disappearance of the local inflammation. After continuous treatment C.R.P became negative in four months and the bacterial flora inactive (negative) The nasopharyngeal treatment with 1 $ZnCl_2$ had been continued for about one year every other day or twice weekly At the end of the year it was carried out once a week. (Since the treatment was experimental, the same method had been employed throughout the period.) No recurrence was observed in this patient after being cured.

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Assessment of clinical results is carried out in accordance with the following criteria

Cured	No appearance of arthritic symptoms for over three years. (Informal cases for over 5 years) Disappearance of objective symptoms of arthritis and normal temperature has been maintained. Improvement of serum reaction.
Improved	Alleviation of arthritic symptoms as compared with those before treatment and recovery to normal activity Attainment of lowering of the body temperature. Serum levels unsatisfactory
Unchanged	No improvement has been attained in arthritic symptoms and other clinical findings.

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7	inflammation (+)	+++	++
8	inflammation (+)	+	−
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Concurrent treatment	(−)	10
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local treatment he got well. Disappearance of the symptoms brought disappearance of the local inflammation. After continuous treatment C.R.P became negative in four months and the bacterial flora inactive (negative) The nasopharyngeal treatment with 1 ZnCl₂ had been continued for about one year every other day or twice weekly At the end of the year it was carried out once a week. (Since the treatment was experimental the same method had been employed throughout the period.) No recurrence was observed in this patient after being cured

Treatment of Rheumatism as a Complication of Nasopharyngitis

As mentioned previously moderate to severe asopharyngitis without manifest subjective ymptoms has been detected in 80% of normal ersons but a latent inflammatory focus always xists in rheumatic patients. Table 33 shows e results of the examinations in 14 randomly lected cases.

The patients with rheumatism were treated r nasopharyngitis in our ORL clinic and 15 ses of chronic arthritis and 9 cases of rheumatic ver were selected for the study All other edications were discontinued except the local eatment of nasopharyngitis with 1 % $ZnCl_2$ lution and the patients response to the treat ent are indicated in Table 34

Assessment of clinical results is carried out in cordance with the following criteria.

Cured	No appearance of arthritic symptoms for over three years (Informal cases for over 5 years) Disappearance of objective symptoms of arthritis and normal temperature has been maintained Improvement of serum reaction.
Improved	Alleviation of arthritic symptoms as compared with those before treatment and recovery to normal activity Attainment of lowering of the body temperature. Serum levels unsatisfactory
Unchanged	No improvement has been attained in arthritic symptoms and other clinical findings.

T bl 33 Grade of inflammation of nasopharyngitis in rheumatic cases.

Cases of rheumatism	Nasopharyngitis: smear preparation	abrasion pain	abrasion bleeding
1	inflammation (+)	++	−
2	inflammation (+)	++	
3	inflammation (+)	+	−
4	inflammation (+)	++	+
5	inflammation (+)	++	+
6	inflammation (+)	++	+
7	inflammation (+)	+++	++
8	inflammation (+)	+	
9	inflammation (+)	++	
10	inflammation (+)	+++	+
11	inflammation (+)	++	+
12	inflammation (+)	++	++
13	inflammation (+)	++	+
14	inflammation (+)	++	−

Table 34 Results of the nasopharyngeal treatment in rheumatism.

1) 22 cases of chronic rheumatoid arthritis	
Cured	6 cases
Improved	7 cases
Rather improved	6 cases
Unchanged	3 cases
2) 9 cases of rheumatic fever	
Cured	6 cases
Improved	3 cases
Unchanged	0

Certain cases did not pass three years from commencement of the treatment. Some were transferred from the improved group to the cured group

Degrees of chronic rheumatoid arthritis are classified according to the Steinbrocker classification into grades I II and III In the grade I group a considerable number of complete cures could be seen, but in grades II and III good results could not be expected and especially the patients of grade III with deformed joints did not respond to the treatment Alleviation of pain was the best result we could expect in these patients

In contrast patients belonging to grade I responded fairly well to the treatment As shown in Table 35 five out of 11 were cured Most of them maintained a normal state for a long time As shown in Table 36 favorable answers were returned to us from the patients who were cured three years ago

As shown in Table 37 we studied 9 cases of rheumatic fever Some of them showed a good response to the treatment in one month but

introduced her to our clinic on account of impairment of the vocal organ. ORL examination failed to detect abnormality other than a hoarse voice when tired.

Clinical findings She developed a clear cut, butterfly shaped rash which was symmetric. She complained of no itching and the symptoms corresponded to the diagnosis given by the dermatologist. To our regret, no detailed renal examination was made except the diagnosis of albuminuria. The pharynx showed a chronic inflammation with slight edema and rash on both sides of the vocal cords. Nasopharyngeal observation indicated abrasion pain and slight post abrasis hemorrhage. The smear preparation revealed a medium inflammatory picture.

Treatment All dermatological medication and treatment was discontinued except application of 1% $ZnCl_2$. For the first few days she complained of severe pain from abrasion and bleeding was observed. On the 5th day of the treatment she reported remission of the redness in her face. Immediately after the treatment facial redness disappeared, but soon returned to its former state. It seemed that the patient told him that the lesion in the face was much improved. (No effect was obtained while she was admitted to the dermatology department.) Since then the treatment was continued every other day and after one and a half months she left the hospital and returned home. Three months later she visited us again and was admitted to the clinic as she had developed rash in the face. The nasopharyngeal treatment had been continued every day. Respondent to the treatment, exfoliation was observed and the redness disappeared gradually. After three months treatment albuminuria turned to negative and complete remission of the rash was attained. In the fourth month she left the clinic. The patient reported no recurrence and after three years she looked younger than before.

Besides this case two other cases of erythema on the face were observed. It is obvious that the nasopharyngeal treatment has significant therapeutic value for the treatment of S.L.E. It is evident from the observation of immediate remission of redness (in one to two seconds after abrasion) and flushing (after 5 to 6 seconds). Because of their apparent antigen-antibody reaction, systemic lupus erythematodes and rheumatism are classified as autoimmune diseases, but there has been no essential treatment discovered for these diseases except natural recovery. In this relation we can explain that natural remission of nasopharyngitis was closely related to natural remission of S.L.E. or rheumatism. It is interesting to note that an artificial process such as nasopharyngeal treatment could have an influence on these diseases.

3) Sclerodermia

Sclerodermia also may be included in the indication. We observed three cases of sclerodermia and obtained softening of the skin after the nasopharyngeal treatment. In one case prolonged stiffness of the hand which is often observed in rheumatic patients, was completely cured. From this observation a relation between sclerodermia and erythema became evident.

4) Nephritis

There has been no essential treatment found for nephritis except natural recovery like those diseases mentioned above. Natural recovery is often observed in acute nephritis. It is therefore necessary to judge the effect of the treatment by means of controlled study. The nasopharyngeal treatment for fragile infants is useful in preventing them from catching cold. In parallel with the recovery albuminuria often disappears. In the following a case report of a 64 year old female with chronic nephritis will be recounted.

Case No. 4 (Fig. 55)

H.S.L. A 64 year old female. Chronic nephritis.

Chief complaint Appearance of albuminuria and hypertension.

History She had been susceptible to common colds in her infancy and used to complain of throat pain, but usually with no abnormal fever. When she was at the age of 59, she was diagnosed as having nephritis after laboratory examination. The prescribed diet was given. Six years ago she was admitted to hospital for systemic examination and again chronic nephritis was diagnosed (albuminuria (+) but RBC (±)). Hemorroids were also detected. For three years since then she had been examined for her albumin status which showed positive. Finally the value of albuminuria reached to (±) and she underwent a tonsillectomy. The result of the operation was excellent and albuminuria was reduced to trace condition. After six months proteinuria increased to positive and about one year ago she visited this clinic. Systemic examination at the time of her visit to our clinic showed blood pressure of 150-110 mmHg and proteinuria was recognized after four drops of sulfosalicylic acid added to the urine. Urinary sedimentation was normal with

a marked inflammation and the local treatment of nasopharyngitis alone lead to a significant recovery from the disease In these instances, nasopharyngitis was laent and because of the lack of subjective symptoms very little medical attention has been directed to it *It is important* to demonstrate the mechanism of the cure process in the course of the nasopharyngeal treatment in the rheumatic patients.

A relationship between the inflammatory focus and autoimmune disease or collagen disease has been suspected by many investigators. In view of the prolonged sensitization concept (OKABAYASHI) a causal relation between them has already been established Clinical observation of nasopharyngitis indicates that the nasopharyngeal treatment has a significant therapeutic value for rheumatism.

The mechanism of cure may be considered from various angles.

1 Removal of the infectious source

2 Secration of steroid (11 OHCS) in blood due to stimulation of the nasopharyngeal mucosa

Application of Nasopharyngeal Treatment for the Purpose of Withdrawal from Corticosteroids

It is considered that the nasopharyngeal treatment is a more useful therapy for rheumatism than steroid treatment From this concept we may facilitate termination of steroid treatment and save the patients from the side effects of corticosteroids by employing this treatment

A steroid derivative 11 OHCS is excreted into the blood upon stimulation of the nasopharynx. The amount of excretion is considered optimum, so that administration of steroids can be discontinued at an early stage of the nasopharyngeal treatment There is no knowing when to discontinue steroid administration, but the author believes it is advisable to stop it at the earliest possible time if no risk is anticipated from the termination I would rather recommend if the nasopharyngeal treatment is safely employed in place of steroid therapy to discontinue the steroid therapy In addition the problem of shock is considered an iatrogenic disease due to administration of steroids. It is reported that serious shock states were caused in patients while operating but the reason for the shock has not been confirmed

The relation between the excretion of 11 OHCS and nasopharyngeal stimulation, as explained above, must be referred However prolonged steroid treatment and the patients with atopic allergic symptoms showed a lowering of 11-OHCS excretion after nasopharyngeal stimulation. Such a reversive phenomenon can be rectified by continuous nasopharyngeal treatment. The author assumes such reversible phenomenon may be related to a shock state.

So far we have discussed clinical observations on rheumatism and nasopharyngitis. Since we think that the presence of nasopharyngitis in a large number of people may play a role in inducing disease like rheumatism of which the pathogenic cause is unknown it is necessary to go further to study the effect of the nasopharyngeal treatment in the patients with diseases like rheumatism.

The following pages will show two or three cases of clinical experiments with nasopharyngeal treatment.

2) Systemic Lupus Erythematodes (SLE) OKABAYASHI explained that S.L.E. may be induced as a result of prolonged sensitization (1963) We discuss the clinical results obtained by nasopharyngeal treatment for the patients with S L.E. Nasopharyngitis is characteristic *with its chronic inflammatory focus*, and if S L.E. can be cured by the treatment of such inflammation it is quite interesting from the clinical standpoint

Case No 3

C.K. A 50 year old female with S.L.E.

Chief complaint Persistent erythema of the face

History She noticed redness in the face when she felt tired. (July 1964 two years before the first examination at this clinic.) The erythema was present between the eyes and its size was about 2 cm² The shape was irregular The erythema was clearly defined with marked redness. After six months she was diagnosed as having lupus erythematodes but she did not respond to treatment. In November 1965 erythema developed in both her hands and extended to the neck and chest. She visited another university *hospital* and was admitted for two months but no improvement was attained. Around that time she felt pain in the finger joints and rehumatism was diagnosed at the orthopedic department. A dermatologist

the body Tonsillitis and carious teeth are considered to cause focal infection Such causal relationships are often referred to tonsillitis and rheumatism, or tonsillitis and nephritis. Chronic rheumatoid arthritis is often taken up as a target since the onset of pain in joi ts and other portions of the body becomes a guide post for the clinical course. In other words, assuming that tonsillitis is cause of rheumatism, we will stimulate the tonsils and examine whether rheumatic symptoms are aggravated or not or na ena. If symptoms of tonsillitis are related to the pathogenic process of rheumatism, tonsillectomy may be indicated. In the case when tonsillitis is determined as an infectious focus, for example in rheumatism, a h gh percentage of cures may be expected following tonsillectory However it is not always p-plicable to rheumatism or nephritis of nknown etiology The concept of focal infection has one weak opint that is, a chronic inflammation foucs is not always present in these diseases. Therefore tonsillectomy is not alway a useful treatment for rheumatism.

Autoimmunity is a phenomenon discovered in relation to hemolytic anemia in 1946. Burnet completed the theory in 1960 I the development of the theory serum gamma globulin and fluorescei antibody technique ha played an important role. Chronic inflammation focus lso play an important role in the study of tommune diseases

Okabayashi (1963) explained that infection or stimulation from the outside acts directly as heteroimmune but repeated stimulation from outside will be finally transformed to to-immunity This is called *delayed hypersensitivity* Delayed hypersensitivity will occur in the bone marrow spleen and the liver in which reticular cells exist Persistent stimulation is ndispensable in tommune reactions. A chronic inflammation focus is one of the important origins of stimuli and no other nvolvement of factors are considered.

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2 Rheumatic fever
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In discussing focal infection autoimmunity and collagen disease a chronic inflammatory focus should be the prime consideration The presence of chronic inflammation may cause allergic damage to various organs in the form of delayed sensitization The postulation is that chronic inflammation as a cause of persistent infection is nothing but nasopharyngitis.

The causal relationship is always observed by pathohistological examination. Clinically we observed that 80% of 4 000 subjects developed more than moderate inflammation in the nasopharynx. Inflammation of the tonsils or gums always accompanies intense nasopharyngeal inflammation, but this is not always associated with those. It is often observed that nasopharyngeal treatment educes remission of the inflammatory symptoms of tonsillitis. This is true also of alveolar pyorrhea. Toothache originating from acute inflammation of the dental root easily responded to nasopharyngeal treatment.

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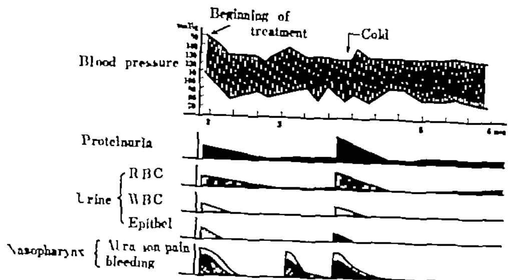


Fig. 55. Case No. 4 H. M 64 Y o M

four to five RBC and the same amount of WBC and epithelial cells. However nasopharyngeal observation revealed presence of an intense inflammation and a post abrasive hemorrhage with a severe abrasion pain.

Clinical course Daily nasopharyngeal treatment *with 1 $ZnCl_2$ had been exercised* and the clinical course was observed At first she complained of abrasion pain, but it gradually decreased and in two weeks almost no abrasion pain was present. During that period blood pressure dropped from 140–130 to 90–80 mmHg and proteinuria could be recognized only with six drops of sulfosalycylic acid. RBC count was two to three and in three weeks after the treatment it disappeared. After two months she caught cold and discontinued treatment for one week. The reexamination disclosed that proteinuria increased to react to two drops of sulfosalycylic acid and a large number of RBC WBC and epithelial cells appeared. The nasopharyngeal observation indicated the presence of intense inflammation with a severe abrasion pain and bleeding The smear preparation also showed the existence of marked inflammation. The treatment had been continued for 20 days and her nasopharyngeal condition and albuminuria improved. She left the clinic to travel abroad. After one year of overseas life she was examined for blood pressure and proteinuria and was quite healthy (Fig 55)

As observed in the above case improvement of albuminuria did not indicate excellent therapeutic response but the worsening of nasopharyngitis ran in parallel with deterioration of albuminuria and this phenomenon was quite interesting The author wishes to obtain more cases like this to study in detail by means of biopsy

However in infants, as mentioned in the foregoing pages, we observed good results in feeble children who habitually caught cold and produced proteinuria It seems interesting to observe the clinical effects of the nasopharyngeal treatment in patients with impaired liver or thyroid gland. The author has not experienced sufficient cases of this category but once observed lowered GOT and GPT after the treatment of nasopharyngitis. Another case was related to reduced basic metabolism due to throidal disorder The treatment successfully achieved normal function of the thyroid gland. In an elevated metabolism case this treatment reduced the function to the normal state It is a desire of the author that readers will further investigate such relations.

Diabetes mellitus is also an interesting theme of the nasopharyngeal treatment The pathogenic mechanism of diabetes is still in question but some clinicians think that impairment of the pancreas in the diabetic may be related to autoimmune diseases and from this standpoint we might find some clinical clues in the treatment of diabetes.

5) Nasopharyngitis as an Infectious Source

The term focal infection was first used by Frank BILLINGS in his report carried in JAMA in 1938 to explain the onset of infection by intrusion of bacteria persisting in some part of

the body Tonsillitis and carious teeth are considered to cause focal infection Such causal relationships are often referred to tonsillitis and rheumatism, or tonsillitis and nephritis. Chronic rheumatoid arthritis is often taken up as a target since the onset of pain in joints and other portions of the body becomes a guide-post for the clinical course. In other words, assuming that tonsillitis is cause of rheumatism, we will stimulate the tonsils and examine whether rheumatic symptoms are aggravated or not or vice versa. If symptoms of tonsillitis are related to the pathogenic process of rheumatism, tonsillectomy may be indicated. In the case when tonsillitis is determined as an infectious focus, for example in rheumatism, high percentage of cures may be expected following tonsillectomy However it is not always applicable to rheumatism or nephritis of unknown etiology The concept of "focal infection" has one weak point, that is, a chronic inflammation focus is not always present in these diseases. *Therefore tonsillectomy is not always a useful* treatment for rheumatism.

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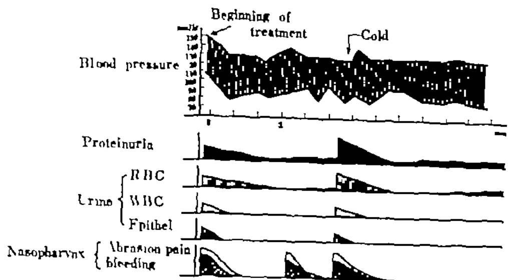


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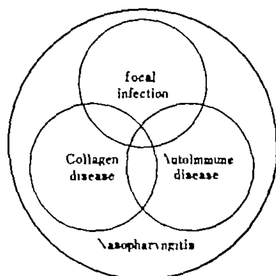


Fig 56.

etiological basis. From the point of the focal infection assumption of the infection site is important so the existence of antibodies is the primary problem in autoimmunity (Fig 56)

Examination of inflammatory foci closely related to nasopharyngitis indicated that infection or antibody reaction are not the primary objects of the study of the pathogenic process of collagen disease since they do not represent histopathological aspects of collagen diseases.

The pathogenic process of nasopharyngitis demonstrates close relationships to secondary infections. Some clinicians are trying to investigate relations between nasopharyngeal treatment and clinical courses of allergic diseases.

So far as his consideration concerns, the author would like to introduce to these secondary inflammations (focal infection, autoimmune disease or collagene disease) the thought of "**Inflammation Without Infection** which is controled remotely from the other infectious part (like nasopharyngitis) (Of course these inflammation without infection may sometimes have the second infection of bacilli such as nephritis)

2. Significance of Nasopharyngitis in Infectious and Allergic Diseases of Unknown Origin

1) Habitual Aphthosis

Habitual aphthosis has been thought to occur in vitamin deficiency in gastrointestinal disorders, common cold or after drinking, but there is no conclusive evidence. The author examined the nasopharynx of the patients and the observed presence of intense inflammation in their nasopharyngeal cavity. The treatment of the nasopharyngeal cavity reduced the inflammation.

Case No. 5

Y.K. 32 year old male. Habitual aphthosis.

Chief complaint: Pain in the mouth. He suffered from hooping cough at age of six. Since then he often caught cold. Aphthosis appeared frequently at age of 7–8. Its duration used to be 10–14 days. Various efforts were in vain.

Clinical findings: Aphtha of 3 mm in size appeared on the left buccal mucosa and there were 2 aphthas on the lower gums with severe pain. Abrasion of the nasopharynx produced pain and bleeding. The pain persisted for 5 hours. The smear sample from the nasopharynx indicated desquamation of ciliated epithelial cells and presence of wandering leucocytes and proliferation of bacteria. The presence of erosion at the nasopharynx was also demonstrated.

Clinical course: All medications were discontinued except the nasopharyngeal treatment with 1 ZnCl (with small amount of anesthetic added). The treatment was carried out once daily. The first treatment reduced the pain and white ulcers diminished in 4–5 days. Prolonged treatment diminished aphthosis and the ulcers became atypical. The patient has never experienced aphthosis since his complete recovery.

Habitual aphthosis is difficult to cure completely. It sometimes stops producing any symptoms for unknown reasons. In the past we reported 19 cases of aphthosis treated by means of nasopharyngeal treatment.

Table 38 shows the degrees of nasopharyngitis and the frequency of aphthosis. It indicates that in habitual cases accompanied with severe inflammation and abrasion pain, nasopharyngitis was intense. In slight aphthosis, nasopharyngitis was also mild. Table 39 illustrates the relation between the number of lesions of aphthosis and the severity of nasopharyngitis. Table 40 shows the clinical value of the nasopharyngeal treatment in reducing frequency of aphthosis. Assessment of effectiveness is given to cases which had been free from the recurrence of aphthosis over six months of observation. It is generally observed that the nasopharyngeal treatment will improve symptoms, but in some cases periodical recurrence

Table 38 Severity of nasopharyngitis and frequency of aphthosis.

Aphthosis	Nasopharyngitis		
	Severe	Mild	Almost none
more than twice/month	5	0	0
once/month	0	4	2
once/2 month	1	6	1

Table 39 Severity of nasopharyngitis and numbers of aphtha.

Nos. of Aphthosis	Nasopharyngitis		
	Severe	Mild	Almost none
more than 1 at time	5	1	0
one at time	1	9	3

Table 40 Results of the treatment of aphtha and nasopharyngeal abrasion pain.

Effectiveness of the treatment	Nasopharyngeal abrasion			
	Disappeared	Slightly effective	Unchanged	No abrasion pain
effective	7	1	0	1
slightly effective	1	1	0	0
no effect	1	0	4	3

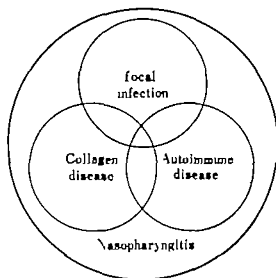


Fig. 56.

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10th day the abrasion pain was reduced and at the same time the headache was alleviated. Radiation of the pain to the teeth also decreased. After 20 days the abrasion pain and bleeding were completely healed. After two months marked improvement was observed and in 6 months complete cure was recorded.

Ten cases of primary alveolar pyorrhea (bleeding from gums) were treated with the nasopharyngeal treatment, the results of which are shown in Table 41. Table 41 shows the clinical value of local treatment in the cases of alveolar pyorrhea. Assessment of the efficacy of the treatment was made by comparing the amount of bleeding before and after the treatment (Fig 57)

4) Gastric Ulcer

As discussed in the previous pages, gastric ulcer was treated by nasopharyngeal treatment and

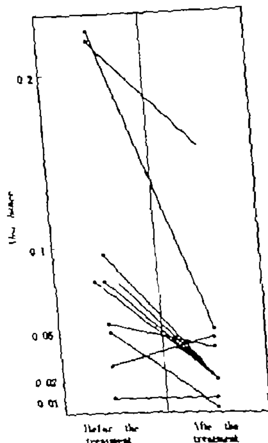


Fig. 57 Comparison in amount of bleeding before and after the nasopharyngeal treatment

good results were obtained. The following is a case report.

Case No. 7

S.S. A 49 year old male. Gastric ulcer and diabetes mellitus.

Chief complaint Gastric ulceration and dryness of the mouth.

History Gastric ulcer was diagnosed 10 years previously and several examinations had been carried out with the same results. Gastroscopy showed an ulcer. Diet and medication failed to improve it. Recent gastroscopy showed a 1.5cm ulcer in the gastric mucosa. The patient also developed diabetes mellitus.

Clinical course All medications were discontinued except nasopharyngeal treatment with 1% $ZnCl_2$. Intense abrasion pain and bleeding were observed. On the 5th day the pain and bleeding decreased and in 10 days, NP indicated disappearance of the niche with no epigastric pain and occult blood. Gastroscopy showed normal gastric mucosa and after two years no abnormality was found in gastroscopy. Diabetes mellitus was also healed, but this case will be discussed later in another part of this report. A total of 5 cases of gastric ulcer were shown to be recovered in NP and gastroscopy. In duodenal cases similar results were observed. Relapse was rare if sufficient treatment was given.

The above cases were relatively mild ones and we cannot conclude that nasopharyngeal treatment would be effective in cases requiring surgical operation, but we consider it effective in post operative ulcers.

5) Other Chronic Inflammations

In the foregoing pages we have referred to the effectiveness of treatment in rheumatism and phthisis of so-called non-suppurative inflammation.

The concept of focal infection, autoimmunity and collagen disease is directly related to the pathogenic process of nasopharyngitis and secondary infection is considered to be induced by the presence of a chronic inflammatory focus. This will be explained in the case of chronic habitual parotitis in children.

Case No. 8

R.H. 10 year old girl. Chronic parotitis.

Chief complaint Relapsing parotitis

History Swelling and pain were felt in the left parotid gland. After a cold, excretion of pus from the left side cheek was detected. Occasional swelling of the parotid was repeated. Pediatrists and otorhinologists prescribed antibi-

was noted. Continuous treatment reduced the frequency of aphthous to zero despite the deterioration of nasopharyngitis. Clinical phenomena such as this case can be observed in other diseases. Complete non recurrence state for the observation period is assessed as complete cure. In this table at least 7 cases out of 19 were cured completely and this result is interesting since the nasopharyngeal treatment is as useful as the steroid treatment.

Pathologically aphthous is a minor ulceration of the oral mucosa and no etiology has been established but this disease has the following characteristics.

1 The appearance of ulcers is related to the progress of nasopharyngitis.

2 Ulceration of aphthous is considered to be of non bacterial origin or to be an inflammation due to secondary infection.

Gastric ulcer or duodenal ulcer may be included in this category and the nasopharyngeal treatment has been observed useful for the treatment of diseases of this category Gastric ulcer or duodenal ulcer are considered due to autonomic nerve disorders. Consideration on these diseases will be made in a later chapter

2) Behçet's Disease

We have studied two cases of Behçet's disease. One case had marked improvement in 10 days after the start of the nasopharyngeal treatment and the clouded aqueous humor recovered its clarity but the patient did not come to our clinic any more Another case was a confirmed case of Behçet's disease as diagnosed by an oculist. However no ocular symptoms appeared at time of the patient's visit to this clinic, except persistent aphthous. Aphthous was cured by the treatment of nasopharyngitis.

Behçet's disease although it is a relative to aphthous, causes severe ocular impairment and the symptoms are more intense than aphthous.

To our regret we have seen only two cases of Behçet's disease, but one case responded excellently to the nasopharyngeal treatment and aphthous was cured completely Group trials for Behçet's disease are being prepared, and we expect good clinical results from the nasopharyngeal treatment.

3) Alveolar Pyorrhea

Case No. 6

S K. A 36 year old male. Alveolar pyorrhea.

Chief complaint Headache dizziness, but alveolar pyorrhea was not the chief complaint.

History Severe headache had been experienced for several years with occasional dizziness. Alveolar pyorrhea was observed on the mandible and three incisors needed extraction.

Clinical course Nasopharyngitis had not been detected but the abrasion preparation indicated the presence of intense inflammation of the pharynx. Application of 1 $ZnCl_2$ with local anaesthetics to the nasopharynx produced bleeding which continued for 4 hours. During the nasopharyngeal treatment pain radiated towards the maxilla and mandible and the patient felt as if the root had been lifted. A similar sensation was felt the next day after the treatment. After the 5th day of treatment he noticed pyorrhea begin to decrease On the

Table 41 Cases of gingival bleeding and gingival pain.

Case No.	Age	Sex	Main symptoms	Nasopharynx		Picture of epithelium smear preparations (inflammation)	Duration of treatment	Effectiveness
				Abrasion	Bleeding			
1	38	[illegible]	Gingival bleeding, gingival pain	++	++	intense	1 month	dramatic
	25	[illegible]	Gingival bleeding	++		–	1 month	effective
3	23	♂	Gingival bleeding gingival pain	+++	++	intense	1 month	dramatic
4	[illegible]5	♂	Gingival bleeding	++	–	moderate	1 month	no effect
5	19	♂	Gingival pain		+	–	1 month	dramatic
6	29	[illegible]	Gingival pain	++	+	moderate	1 month	effective
7	39	[illegible]	Gingival bleeding	+	++	moderate	1 month	effective
8	16	♀	Gingival pain	++	+	moderate	1 month	no effect
9	26	♀	Gingival bleeding	+	++	moderate	1 month	dramatic
10	32	♀	Gingival bleeding	++	++	moderate	1 month	no effect

10th day the abrasion pain was reduced and at the same time the headache was alleviated. Radiation of the pain to the teeth also decreased. After 70 days the abrasion pain and bleeding were completely healed. After two months marked improvement was observed and in 6 months complete cure was recorded.

Ten cases of primary alveolar pyorrhea (bleeding from gums) were treated with the nasopharyngeal treatment, the results of which are shown in Table 41. Table 41 shows the clinical value of local treatment in the cases of alveolar pyorrhea. Assessment of the efficacy of the treatment was made by comparing the amount of bleeding before and after the treatment (Fig. 57).

4) Gastric Ulcer

As discussed in the previous pages, gastric ulcer was treated by nasopharyngeal treatment and good results were obtained. The following is a case report.

Case No. 7

S.S. A 49 year old male. Gastric ulcer and diabetes mellitus.

Chief complaint: Gastric ulceration and dryness of the mouth.

History: Gastric ulcer was diagnosed 10 years previously and several examinations had been carried out with the same results. Gastroscopy showed an ulcer. Diet and medication failed to improve it. Recent gastroscopy showed a 1.5cm ulcer in the gastric mucosa. The patient also developed diabetes mellitus.

Clinical course: All medications were discontinued except nasopharyngeal treatment with 1% $ZnCl_2$. Intense abrasion pain and bleeding were observed. On the 5th day the pain and bleeding decreased and in 10 days, XP indicated disappearance of the niche with no epigastric pain and occult blood. Gastroscopy showed normal gastric mucosa and after two years no abnormality was found in gastroscopy. Diabetes mellitus was also healed, but this case will be discussed later in another part of this report. A total of 5 cases of gastric ulcer were shown to be recovered in XP and gastroscopy. In duodenal cases similar results were observed. Relapse was rare if sufficient treatment was given.

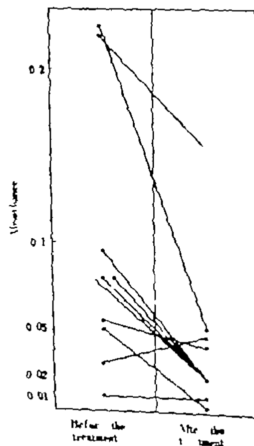


Fig. 57 Comparison in amount of bleeding before and after the nasopharyngeal treatment

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Chief complaint: Relapsing parotitis.

History: Swelling and a pain were felt in the left parotid gland. After a cold, excretion of pus from the left side cheek was detected. Occasional swelling of the parotid was repeated. Pediatrics and otorhinologists prescribed various

antibiotics but the patient failed to improve. When she visited our clinic, excretion of pus under pressure from the left parotid gland was observed No salivary calculus was found in XP but intense inflammation in the duct was observed. A number of staphylococci aureus were discovered in the pus. Nasopharyngeal examination produced abrasion pain and bleeding The smear preparation showed the presence of intense inflammation

Clinical course All other medications were stopped except the nasopharyngeal administration of 1% $ZnCl_2$. The abrasion pain and bleeding continued for about one month From the start of the treatment the swelling began to decrease and excretion of pus had almost disappeared on the 5th day of the treatment The patient was treated for another 6 months and a slight relapse was noted after 2 months of treatment, but continuous therapy inhibited the recurrence of the symptoms.

We experienced three other cases of *parotitis* which took a similar clinical course. *In this* chapter attention was paid to the fact that the chronic inflammation focus existed and excreted a large number of *infectious micro-organisms*. *In* these chronic inflammatory diseases we often found that nasopharyngeal *treatment* achieved successful results in cases like chronic otitis media, chronic rhinitis chronic pharyngitis and chronic nasopharyngitis. It also produced excellent results in acute cases of these chronic inflammatory diseases but when *they* were in the silent state, the treatment was less effective or took much time to alleviate the symptoms, as in the case of chronic sinusitis. It is interesting to see that it is clinically effective in the treatment of inflammation originating from injection of microorganisms.

6) Allergy

Allergic rhinitis is one of the commonest disease of otorhinolaryngology PIRQUET first reported antigen antibody reaction as a cause of allergy and some investigators, such as Hansel include allergic rhinitis among the typical allergic cases because of the positive intracutaneous reaction and provacative reaction of nasal mucosa and marked increase of eosinophilic leucocytes in nasal fluid and in the blood

The author observed a number of cases showed negative intracutaneous reaction despite repeated recurrence of allergic nasal symptoms. In some cases eosinophilia was noted while in others it was not. Hyposensitization therapy is considered useful since reagin and blocking antibody are observed in the patients. However the author postulates that reagin *or blocking* antibody production is nothing *but a biological* phenomenon and hyposensitization therapy cannot attain a complete cure. The fundamental rationale is that the author *places* importance on the presence of nasopharyngitis in allergic rhinitis. The observa*tion* of clinical conditions disclosed that the patients first had an unusual feeling at the soft *palate* and sniffling followed The unusual feeling at the soft palate indicates the existence of abnormal conditions. Some patients told us they had a cold and recurrence of the cold symptoms formed a habituation From the clinical findings as such it is reasonable to consider the relationship between nasopharyngitis and allergic rhinitis. We examined nasopharyngeal conditions in randomly selected patients, and the results are shown in Table 42 As shown we confirmed the existence of an intense inflammation or erosion in the nasopharynx. Encouraged by these findings, we carried out the local treatment of the nasal abrasion with 1 % $ZnCl_2$ solution and recorded the results.

Case No. 9 (Figs. 58, 59)

K.T A 25 year old male Allergic rhinitis.

History The patient had been suffering from chronic allergic rhinitis for three years mostly

Table 42 Nasopharyngeal findings of allergic rhinitis.

Case No.	Abrasion pain	Abrasion bleeding
1	+++	+++
2	+++	+++
3	++	++
4	++	++
5	+++	+++
6	+++	++
7	+	+
8	+	++
9	+	+
10	+++	++
11	++	+
12	+++	+++
13	+++	+++
14	++	++
15	++	++
16	+++	+++
17	+++	+++
18	++	+
19	++	+++

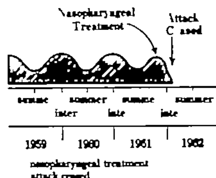


Fig. 58. *Course of the symptoms by years* (Case No. 9)

in winter but occasionally in summer. Nasal obstruction and rhinorrhea fluid had been persistent and pallid swelling of the nasal mucous was observed. Laboratory data indicated 80% presence of eosinophil leucocytes in the nasal fluid and 700 pcs. in the blood. A severe postabrasion hemorrhage and marked exfoliation of ciliated epithelium, appearance of wandering leucocytes and proliferation of staphylococci aureus were noted.

Clinical course. According to the patient, antihistamine and other anti-allergic preparations had no effect. The usual nasopharyngeal treatment alone was prescribed and other treatment was discontinued. No bleeding was observed on the 10th day of the treatment and abrasion pain disappeared on the 14th day. Continuous treatment obtained growth of epithelial cells and on the 60th day the growth of normal ciliated epithelia was observed. Allergic symptoms had almost disappeared on the 35th day. On the 100th day eosinophils, as shown in Figs. 58, 59, disappeared, and all symptoms also disappeared.

Table 43 shows the clinical results of the nasopharyngeal abrasion in allergic cases. As shown in Table 44 6 cases were completely cured, 9 cases improved and 4 cases were unchanged. The complete cure meant recovery of normal values of eosinophil leucocytes in nasal fluid and blood. Alleviation signifies that the clinical symptoms were reduced enough in severity to allow the patients to return to work and recovery of eosinophil leucocyte values to the normal standards. An interesting clinical observation, that is a marked imporvement of asthma, urticaria, atopic dermatitis and food allergy was made, and from these results the local abrasion treatment is not only useful in allergic rhinitis but also in other diseases complicated by allergy.

Gamma Globulin Alteration

Clinical usefulness of nasopharyngeal abrasion in the treatment of allergic rhinitis and other allergic symptoms, and normalization of eosinophil leucocyte values were described in the preceeding pages. As mentioned already clinical patterns of allergic symptom are not always accompanied by antigen-antibody reactions, but

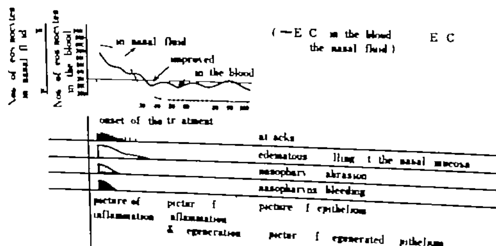


Fig. 59. *Clinical course* (Case No. 9). Allergic rhinitis K.T. 25 y. o. M.

Table 43. Result of the treatment.

Case No.	Duration of observation	Eosinocyte in nasal fluid: before the treatment	Eosinocyte in nasal fluid: after the treatment	Effect
1	8 months	++	−	cured
2	6 months	++	+	improved
3	6 months	++	−	cured
4	10 months	+-	++	improved
	1 months	++	+	slightly improved
6	6 months	++	++	improved
7	8 months	++	−	cured
8	8 months	+	−	improved
9	7.5 months	+++	+	improved
10	5 months	++	++	slightly improved
11	months	+++	++	slightly improved
12	20 day	++	++	slightly improved
13	25 days	++	+	slightly improved
14	5 months	++	−	cured
15	2.5 months	+++	+	improved
16	4 months	++	+	improved
17	3 months	++	+	improved
18	1 months	++	+	improved
19	20 days	+++	+	slightly improved

Table 44. Accumulation of the results.

	Number of cases
Slightly improved	6
Improved	9
Cured	4
Total	19

only by eosinophilia. In general the cases with antigen antibody *reaction are called nasal allergy* and others are called vasomotor rhinitis to *distinguish* between them. However if we place importance on the clinical *findings* we should reconsider the significance of antigen antibody reaction in allergic rhinitis. We have studied how the nasopharyngeal treatment affects antigen antibody reaction. The clinical experiments were carried out to examine the alteration of immune globulin in two groups of patients, one group was exclusively treated with nasopharyngeal abrasion and the other with hyposensitization. The experiments were carreid out by TAKAYAMA of our department. Twenty eight patients who showed positive *antigen* antibody reaction were devided into two groups of 14 each. Group A was treated with hyposensitization *and gorup B exclusively with the* nasopharyngeal treatment.

Tables 45 and 46 illustrate the results.

Table 45 represents the results of group A and Table 46 group B. Both groups were treated for 3 months. With the exception of 3 cases, group A showed 11 effective cases including 3 excel*lent and group B showed 12 effective and 2 non* effective cases. A comparison of IgA and IgG before the treatment disclosed that no IgG changes were observed *in either gorup* and the general picture showed no definite direction. In contrast changes of IgA showed an increase after the treatment and no reduction was observed either group. As shown in the table in *7* cases of group A IgG increased after the treatment while group B and 9 cases (64) of elevation.

Clinical Significance of Nasopharyngeal Treatment in Treating Nasal Allergy

We have described how the nasopharyngeal treatment was not only useful in treating nasal allergy but also produced changes in the serum immunoglobulin values. *It is a well-known fact* that a certain type *of allergy reacts sharply to* specific antigen and provokes allergic symptoms. However *we cannot* say that allergy is equal to antigen-antibody reaction for the following reasons.

1. *We observe* some cases lacking antigen antibody raection or eosinophilia despite their typical *allergic onset.*

Table 45 Group treated by hyposensitization.

Case No.	Age Sex	Allergen	Duration of treatment	I A 128	I A 256	I A 32	I G 256	I G 32	Effect
1	44 ♀	Japanese hop	3 mo.						unchanged
2	46 ♂	House dust	3 mo.						effective
3	2 ♀		mo.						dramatic
	27 ♂	Ambrosia	mo.						unchanged
5	34 ♀	House dust	4 mo.						effective
	29 ♀		mo.						unchanged
7	34 ♀		mo.						dramatic
8	21 ♂	Red pine tree	mo.						effective
	43 ♀	House dust	3 mo.						effective
10	32 ♀		3 mo.						unchanged
11	54 ♂		3 mo.						effective
12	36 ♂		3 mo.						effective
13	30 ♂		3 mo.						effective
1	18 ♂		3 mo.						dramatic

Table 46 Group treated nasopharyngeally

Case No.	Age Sex	Allergen	Duration of treatment	I 64	I 128	I 256	I 512	I 64	I 128	I 256	I 512	I 1024	Effect
	34 ♂	House dust	mo.										[illegible]
	37	Japanese cedar	mo.										[illegible]
		House dust	mo.										
	44	Candida	mo.										
		House dust	mo.										[illegible]
			mo.										
			mo.										[illegible]
	18 ♂	Ambrosia	mo.										
	24 ♂	Candida	mo.										
10	29	House dust	mo.										unchanged
		Ambrosia	mo.										[illegible]
12	44	Candida	mo.										
		Ambrosia	mo.										
		Japanese cedar											unchanged

Table 47

Clinical symptoms

Nasal congestion | Watery rhinorrhea | Sneezing | Eosinophilia | Intracutaneous reaction

Allergic rhinitis

Rhino-allergosis

Vasomotor rhinitis

Vasomotor hypertrophic rhinitis

Nasopharyngitis

2. Antibody antigen reaction is explained as a biological reaction of protein or some complex particle, but we can observe that a simple stimulant (for example SO_2) or physical changes such as coldness may provoke allergic symptoms

3 If a biological reaction is considered as an antigen antibody reaction we cannot explain the occurrence of double reaction to different antigens.

4 Hyposensitization therapy is a treatment of allergy by repeated injection of antigen but it increases reagin. Blocking antibody is confirmed but it must be a treatment to make the body accustomed to a stimulant.

5 The usefulness of the non specific therapy or the treatment of anti-chemical mediator may suggest an involvement of factors other than antigen-antibody reaction.

6 Nasopharyngeal treatment is applicable to any allergic symptoms and normalizes eosinophil leucocyte values. It also influences serum immune globulin in the same manner as the hyposensitization treatment.

From the above observations we may conclude that an antigen-antibody reaction may cause allergic symptoms, but it is not the exclusive reason. As explained previously the nasopharyngeal treatment attained good results in nasal allergy responding to the alleviation of nasopharyngitis. From this fact nasal allergy is related to nasopharyngitis in a wider sense than antigen antibody reaction.

Further investigation of the relation between nasopharyngitis and functional disorders of the nasopharynx is explained in Table 48 which includes the cases collected by TAKAYAMA The table contains groups C and D in addition to B Group B consisted of 14 typical allergic cases with intracutaneous reaction, eosinophilia and positive clinical symptoms. Group C consisted of negative intracutaneous reaction, but with clinically positive symptoms and group D was all negative except for clinical symptoms (snuffling and nasal congestion) These 33 cases were treated exclusively by the nasopharyngeal therapy (1 / $ZnCl_2$) and the results were good in all groups. Besides these groups, hypertrophic rhinitis responded well to the treatment. Conchotomy has been used in a rhinitis chronica hypertrophica vasomotorica but persistent relapse is a threat. It often complicates nasopharyngitis but local treatment alone produces good results. Some patients often mistake nasopharyngeal abnormality as a stuffy nose. Since the disorder is not of a physical nature clinical observation discloses normal findings and some clinicians might conclude that the patient had nasal neuritis. However abrasion treatment might satisfy the patient. The sensation of nasopharyngeal disorders should appear on the dorsal portion of the soft palate, but it often radiates to the nasopharynx and makes the patient complain of nasopharyngeal abnormality or nasopharyngeal neurosis. Various types of nasal allergy (including the so-called vasomotor rhinitis) and habitual hypertrophy of the nasal mucosa usually complicates nasopharyngitis and local treatment often alleviates the allergic symptoms. From this observation we may find a causual relationship in nasopharyngitis and the functional disorders of the nose

Effect of the Nasopharyngeal Therapy in Other Allergic Diseases

From the clinical observation of allergic rhinitis we often observe complication of the

Table 48 Results of the nasopharyngeal local treatment in allergic rhinitis.

		Previously mentioned B Group	C Group	D Group
Findings before the treatment	Intracutaneous reaction	+	−	−
	Eosinocyte nasal fluid	+	+	−
	Nasal symptoms	+	+	+
Effectiveness of the treatment	Dramatic	3	4	2
	Effects	9	5	6
	Unchanged	2	2	0
	Worse	0	0	0
	Total	14	11	8

llergic diseases. Bronchial asthma, urticaria and atopic dermatitis are often observed complicated with nasal allergy. We frequently observed alleviation of these complicate allergic symptoms in association with the improvement of allergic rhinitis. Clinical cases representing each complication are described as follows

Asthma

Patients with acute or chronic bronchial asthma often have the complication of a nasopharyngeal inflammation. We carried out clinical experiments in asthmatic patients and observed the results. 14 cases were completley cured. Two cases are described below

Case No. 10

A 72 year old male, with bronchial asthma.

History He had suffered from pediatric asthma at the age of 4, and it lasted till the present as chronic asthma. When the attack was severe, he had to be hospitalized for 2 3 weeks. Attacks had occurred once or twice year but no seasonal occurrence was noted. After various tests he was found slightly sensitiv to home dust, but no specific antigen was detected. Hyposensitization of home dust was tried but gave no results. Various treatments failed t produce good results. He had been prescribed steroid since 5 years previously on constant basis. He used to increase the dose at the onset of the symptoms.

Clinical course He visited our clinic year ago. A slight bleeding and moderate pain were noted at the abrasion test. The smear specimen disclosed the presence of an intense inflammation. 11-OHCS showed decrease after the local treatment. The continuous local treatment with 1 $ZnCl_2$ inhibited the symptoms entirely (The patient alw ys had cough in spite of the steroid treatment.) The steroid was tentatively reduced to one-half and the patient experienced intense coughing. The steroid was increased to the previous level. It was used in combination with nasopharyngeal treatment for 3 months. I was completely terminated after 6 months. The nasopharyngeal treatment is still continuing and no recurrence is observed.

11-OHCS shows an increase of 20% after the treatment.

Case No. 11

A six year old boy with asthma

Chief complaint Stridor

History He often used to catch cold with cough in his early infanthood and t was diagnosed by pediatrist as bronchitis. Three years ago the onset of coughing became severe and frequent and he was admitted to hospital. After two weeks of steroid therapy the symptoms were improved and he left the hospital. After discharge, the symptoms returned and prednisolone was prescribed. He isited our clinic on the recommendation of the pediatric department of the university hospital.

Clinical course All medications were discontinued. (Steroids were to be permitted only when the symptoms were severe but they were not used.)

The nasopharyngeal treatment with 1% $ZnCl_2$ was employed exclusively A marked bleeding was observed at the abrasion test and the boy cried because of severe pain.

By the 10th day no bleeding was observed and the abrasion pain disappeared on the 14th day Coughing was reduced in both frequency and severity after the treatment. The symptoms disappeared in half month. After two months slight cough was observed 3 times, but after 6 months no recurrence was recorded and he was discharged from the clinic.

After six months he again isited our clinic but the treatment of nasopharyngeal abrasion cured the disease in one week. No recurrence has been reported in the past of months.

The above two cases were confirmed to be bronchial asthma after an intensive laboratory examination by specialists. Steroids were prescribed in both cases but failed to cure the chronic symptoms. It seems to us that the nasopharyngeal treatment made t possible to terminate the persistent symptoms.

Nasopharyngeal Treatment for Other Allergic Diseases

The effects of nasopharyngeal treatment for various allergic diseases were assessed in the previous pages. A food allergy which persisted for a long time was cured by the local treatment. In the following cases of urticaria, atopic dermatitis was diagnosed. The author believes that these diseases are directly related to nasopharyngitis and the improvement of the inflammation followed by improvement of the dermatitis may be sufficient to persuade the reader

Case No. 12

A six year old male with urticaria.

History He used to suffer from urticaria without any apparent cause. Rash appeared in the evening or during the night for two to three hours. The patient had frequent dizziness, headache and nausea. He was diagnosed as having an orthostatic disorder after examination. Adenotomy was tried one year previously but brought no results.

2 Antibody-antigen reaction is explained as a biological reaction of protein or some complex particle, but we can observe that a simple stimulant (for example SO_2) or physical changes such as coldness may provoke allergic symptoms

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	Worse	0	0	0
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3 Nasopharyngitis as a Source of Stimulation of the Autonomic Nerve

In the section on the basic study of nasophryngitis, w explained that nasopharyngeal stimulation provokes a contraction of the pulse w e t the finger and the extraordinary contraction gradually returns to normal in parallel with remission of the inflammation.

Nasopharyngeal stimulation also elevates the blood pressure, but it immediately returns t normal as observed in the blood pressure change caused by mecholyl injection If blood pressure changes result in type N after nasopharyngeal stimulation, mecholyl injection produces type N of blood pressure changes, etc Further we explained that in types S and P the abnormal blood pressure types w'll turn to normal in parallel w th the remission of nasopharyngeal inflammation.

The nasopharynx has a close relation w th the utonomic nerve systems and inflammation of the nasopharynx will affect the utonomic nerves. It is assumen that the nasopharyngeal cav ty has an important receptor for the autonomic nerve transmission. The naspoharynx is quite sensitive to utonomic nerve stimulation and the existence of inflammation will promote stimulant ffects and will react intensely t the utonomic nerve timulation.

Biological reaction to a repeated stimulation ma be considered another important factor reducing the threshold of the utonomic nerve. Foreign stimulants may not provoke allergic reaction t first but repetition of stimulation gradually produces hypersensitu ty I reverse this action has been considered useful treating hypersensitivity of the utonomic nerve system. The relation between nasopharyngitis and the utonomic nerves can only be understood when tonomic nerve disorders respond to nasopharyngeal treatment

Nasopharyngeal treatment has unexpected clinical results the treatment of symptoms originating from utonomic nerve disorders as shown below

1 dizziness or vertigo
2. orthostatic dysregulation (O.D)
3. hypotension
4 hypertension
5 allergy
6. neurosis (like enuresis)
7 gastric ulcer

Headache and diabetes mell tus were excluded intentionally

1) Dizziness or Vertigo

The thor formed that most cases of dizziness have latent inflammation in the nasopharynx and dizziness may be improved by the local treatment of nasopharyngitis as the nflammation of the nasopharynx subsided.

Dizziness is associated with autonomic nerve disorders and this is commonly believed to be true, but only a few persons believe t is a fact actually confirmed by evidence Various tests ha e been devised to demonstrate causal relationships between autonomic nerve disorders and the associates symptoms.

As explained already the nasopharyngeal treatment exercised control over the autonomic nerve system Nasopharyngeal stimulation extends the contraction time of the pulse wa e t the peripheral portion of the fingers from 15 seconds t several hundreds seconds according to the indi idual constitution. Prolonged contraction time suggests that the person has arious autonomic nerve disorders such as palpitation headache, thermoparaesthesia and gastrointestinal symptoms. On the other hand contraction time of the pulse wave is often related t the degree of nflammation of the nasopharynx. The local treatment of the nasopharynx generally restores peripheral essel contraction to normal almost permanently And normalization of the plethysmogram and the

Clinical course He complained of severe pain and intense bleeding was observed. The continuous treatment of 1 $ZnCl_2$ produced marked improvement and in one week no bleeding was observed. After two weeks the abrasion pain disappeared.

On the 5th day the symptoms of urticaria were improved. The site of the rash was limited and the pruritic sensation was reduced. About the 10th day he experienced few symptoms and after three weeks almost none. During the treatment he had rash on the neck and extremities but the symptoms soon disappeared after the treatment During the course of the treatment he had no urticaria for three months and the local treatment was suspended. A month later he had a slight rash around the neck after he ate shrimp.

The treatment was resumed for one month and he was then free from urticaria for three years.

Case No 13

A 55 year old female with atopic dermatitis.

Chief complaint Susceptibility to sumac (lacquer) poisoning

History The patient suffered from sumac poisoning at the age of 17 and she found herself constitutionally susceptible to it thereafter She got a rash whenever she touched poison sumac or lacquered ware such as bowels, chopsticks or other utensils. When the patient was 50 years old she was susceptible to colds. Tonsillectomy was neffective.

Clinical course Nasopharyngeal examination disclosed a severe abrasion pain and bleeding indicating the presence of intense inflammation in the nasopharynx. 1 $ZnCl_2$ twice weekly was prescribed for the local treatment. All other medications were discontinued. After the treatment she never caught cold and was never confined to bed. Her appetite improved and her constipation was cured. Hypotensive condition was improved. It is interesting to note that the patient had contact dermatitis which was completely cured in six months. She was susceptibl to poison sumac, but after the treatment she could touch it without reaction Since then she did not hav any rash if sl touched lacquered utensils.

From these findings we may assume that the influence of nasopharyngitis is not limited to neighboring organs To clarify the correlation is a problem to be solved in the future but for the time being reduction of 11 OHCS in the allergic onset is an improtant clue to the solution

Significance of Nasopharyngitis in the Treatment of Allergic Diseases

Let us consider the mechanism of allergic symptoms apart from the antigen-antibody reaction Nasopharyngitis exists latently in a large number of people and its exacerbation or improvement continues daily A common cold is the worst case and a complication of nasal symptoms is called acute catarrhalic rhinitis. Clinically it closely resemble to allergic rhinitis except that catarrhalic rhinitis is (1) not chronic, (2) lacking eosinophil leucocytes and (3) free from antigen antibody reaction

Acute rhinitis usually terminates after several days but occasionally patients catch cold while in bed Such a relapse or exacerbation of cold is always accompanied by acute aggravation of nasopharyngitis. Acute recurrences of nasopharyngitis can be observed frequently in pediatric patients.

At first the symptoms of acute rhinitis show the typical pattern of the disease but repeated recurrence lowers the susceptibility threshold and the onset of nasal symptoms becomes facilitated A transformation of allergic symptoms from the chronic rhinitis is commonly observed (Such phenomena can be observed in other diseases. An infant with chronic common cold which was always associated with thrombopenia was treated by nasopharyngeal abrasion and the chronic cold was completely crued. Since then no thrombopenia was observed The patient if left untreated, might have been developed some serological disease.)

As stated in the previous pages habitual rhinitis can be eliminated without difficulty but negligence might lead to hypersensitivity of the nasal mucosa despite the slightness of the initial symptoms. The author believes that allergies should be regarded as hyperreactivity symptoms. Thus antigen-antibody reaction or eosinophilia could be understood as one process of hyperreaction (The activity of the chemical mediator produced by antigen-antibody reaction should never be denied in any way)

Cutaneous Diseases

Lupus erythematodes or atopic dermatitis were cured by the treatment of nasopharyngitis For the same reason pustulosis scleroderma urticaria and alopecia were improved after the treatment of nasopharyngitis. The author eliminated case reports because of scarcity of cases.

3 Nasopharyngitis as a Source of Stimulation of the Autonomic Nerve

I the section on the basic study of nasophryngitis, w explained that nasopharyngeal stimulation provokes a *contraction of the pulse wa e t* the finger and the extraordinary contraction gradually returns to normal in parallel with *remission of the inflammation.*

Nasopharyngeal stimulation also elevates the blood pressure, but t immediately returns to normal as bserved in the blood pressure change caused by mecholyl injection. If blood pressure changes result in type N after nasopharyngeal *stimulation, mecholyl njection* produces type N *of blood pressure changes, etc. Further w* explained that in types S and P the abnormal blood pressure types will turn to normal in parallel w th the remission of nasopharyngeal inflammation

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Biological reaction to repeated stimulation may be considered *another important factor* reducing the threshold of the a tonomic nerve. Foreign stimulant ma not provoke allergic *reaction t first, but repetition of stimulation* gradually produces hypersensitivity In reverse this action ha been considered useful in treating hypersensitiv ty of the a tonomic nerve *system* The relation between nasopharyngitis and the utonomi nerves can only be understood when tonomic nerv d sorders respond to nasopharyngeal treatment

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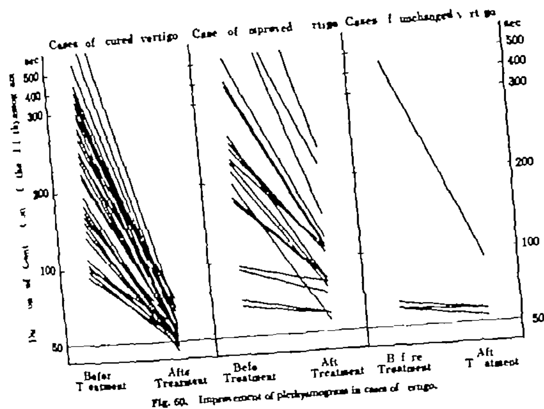


Fig. 60. Improvement of plethysmograms in cases of vertigo.

Table 51 Percentage of cases cured of vertigo as observed by type of change of the blood pressure.

Type of change of blood pressure	No. of cases before treatment of nasopharyngitis	Cured	Improved	Unchanged
S type	34	20 (59%)	12 (35%)	2 (6%)
P type	6	6 (100%)	0	0
N type	14	6 (42%)	6 (42%)	2 (16%)

to dizziness those which belong to types P and S were cured at a higher rate. In contrast, 14 cases of type N indicated poor cure rate as compared to other types.

The assessment of cure of dizziness responding to the nasopharyngeal treatment was made by measuring changes of pulse wave in the finger and the types of blood pressure alteration after the nasopharyngeal abrasion. The cure by the local treatment may be considered due to irritation of the autonomic nerve which was caused by presence of inflammation in the nasopharyngeal cavity.

Table 52 demonstrates the clinical value of nasopharyngeal treatment in patients with dizziness. The patients were subjected to a caloric test before the treatment. The evaluation of the efficacy was made on 35 DP cases, 21

Table 52 Result of the nasopharyngeal treatment in dizziness classified according to vestibular function.

Caloric test	Number of cases	Cured	Improved	Unchanged
DP	35	28 (80%)	3	4
CP	21	12 (57%)	8	1
Normal	29	22 (75%)	5	2
Hyper function	2	1	1	0
Total	87	63	17	7

Table 49 Vertigo.

Cured		Improved		Unchanged	
3 cases	(50%)	3 cases	(50%)	0	
1	(25)	2	(50%)	1 cases	(25)
6	(75)	2	(25)	0	
9	(56%)	7	(44%)	0	
10	(90%)	1	(10)	0	
2	(22%)	4	(44%)	3	(34%)
31	(58%)	19	(35%)	4	(7)

remission of autonomic nerve disorders are closely related.

The possibility of clinical application was tested by FURUYA on 54 cases of dizziness of unknown etiology The nasopharynx of all patients was examined and every one of them had nasopharyngitis The nasopharyngeal treatment with 1 % $ZnCl_2$ solution brought complete cure to 31 cases, improvement of symptoms in 19 cases and 4 cases remained unimproved. The efficacy was 92 6% Table 49 illustrates the results more precisely Efficacy ratings were classifies as complete cure allevia tion of symptoms and unchanged Correspond ing to the symptoms naspoharyngeal inflamma tion was divided into intense medium and mild. The bottom row of the table indicates the num- ber of cures. The highest cure rate was ob- served in the patients with intense nasopharyn gitis (22 cases) and next in those with medium nasopharyngitis. The four unchanged cases inculded 2 mild cases and one with intense nasopharyngitis. The above observation indi cates that dizziness was improved in higher percentage when the nasopharyngeal inflam-mation were severe. Table 50 shows the length of contraction time of the pulse wave measured before and after treatment of naso-pharyngitis in 45 patients and the value of the treatment for dizziness. The left column shows the contraction time of the pulse wave caused by the stimulation of the nasopharyngeal cavity Before the treatment 6 patients had a pulse contraction time of more than 500 seconds and 83 % or 45 cases showed a prolonged contraction time of over 100 seconds. There was no case that had contraction time less than 50 seconds. After the treatment the contraction time was reduced to 300 seconds or less and 44 cases were below 100 seconds.

As indicated in the Table 31 cases were cured 19 improved and 4 cases unchanged. Three out of six cases that had a contraction time of over 500 seconds before the treatment had been cured completely and in the remaining cases dizziness was improved. 29 cases of cure were from the group exceeding 100 seconds and 3 unsuccessful cases belonged to the group of less than 100 seconds. Fig 60 shows the cure rate of dizziness. All of the cured cases show that the plethysmogram returned to normal but in the improved cases the plethysmogram did not always become normal

Table 51 shows the types of blood pressure curve of 54 cases with dizziness before tand after nasopharyngeal treatment Before the nasopharyngeal treatment, 34 cases were type S and 6 type P and 14 cases type N After the treatment 44 cases were type N (normal) 7 type S and there were no types P With regard

Table 50 Duration of reduced amplitude of pulse wave before and after the treatment of nasopharyngitis and results dizziness.

Duration of reduced amplitude by nasopharyngeal stimulation after the treatment					Dizziness					
Duration of reduced amplitud	Before treatment		After treatment		Cured		Improved		Unchanged	
over 501 sec	6 cases	(11)	0		3 cases	(50%)	3 cases	(50%)	0	
401 500 sec.	4	(7)	0		1	(25)	2	(50%)	1 cases	(25)
301–400 sec	8	(15)	0		6	(75)	2	(25)	0	
201 300 sec	16	(30%)	2 cases	(4)	9	(56)	7	(44)	0	
101 200 sec	11	(20%)	8	(15)	10	(90%)	1	(10%)	0	
51 100 sec.	9	(17)	33	(61)	2	(22)	4	(44)	3	(34)
below 50 sec.	0		11	(20%)						
Total					31	(58)	19	(35)	4	(7)

Table 53

Case No. 14 36 yrs. old ♀	Nov. 1968	Dec. 1971 April 1972		
	Before the treatment	Before the treatment	Under treatment	After the treatment
Vestibular function test				
Spontaneous nystagmus	(−)	(−)	(−)	(−)
Static function of the limbs	normal	normal	normal	normal
Caloric test	No abnormality	left side DP		left side DP
Rotation test	No abnormality	within normal limits	normal	normal
Auditory examination	normal	normal		normal
Blood examination, blood chemistry	normal	Total cholesterol 103 mg	normal	normal
ECG (including post effort ECG)	normal	normal	normal	normal
Physical examination	No abnormality	disorders of the autonomic nerve. BP144/70		No abnormality
Respiratory function test		normal		
BMR		+9%		
Nasopharyngeal exam				
Severity of inflammation (exfoliation of the cells, bleeding and brush pain)	intense	intense	Moderate	(−)
Duration of reduced amplitude in pulse wave the finger tip	178 sec.	right 330 sec left 280 sec.	180 sec– 220 sec–	79 sec.
Alteration-curve of the blood pressure		S Type	P Type	N Type
Vertigo	(#)	(#)	(+)	(−)

provement as shown in the diagram and she returned home after three months treatment. No symptoms has been observed until now.

It seems that the case might be a mere psychogenic disease, but if nasopharyngitis had not been detected, it might have been diagnosed as of unknown etiology. Furthermore, if no objective improvement had been observed, the local treatment might have been considered kind of suggestion therapy. Nasopharyngitis has an important relation with the autonomic nerve system, and the fact that autonomic disorders can be improved by nasopharyngeal treatment represents an amazing medical progress (Tables 54, 55).

2) Orthostatic Dysregulation (OD)

The symptoms of orthostatic dysregulation are related to dizziness which originates in postural imbalance. It might be considered reasonable to include "O.D." in the category of diseases with dizziness or vertigo, but in general both symptoms have slightly different meanings. Certain cases of orthostatic dysregulation are not associated with dizziness" and in most cases complications of hypotension, allergic disorders, gastrointestinal impairments will mask the presence of orthostatic abnormality. In this respect the diagnosis of orthostatic dysregulation is almost impossible without the involvement of nasopharyngitis. Orthostatic dysregulation is observed in infants and in middle aged women and the latter cases it is often diagnosed as hysteria or menopausal disorder. In school children almost 10% are said to have this symptom. Despite the importance of this symptom in the pediatric

Table 54. Degree of complication of nasopharyngitis and the result of treatment of vertigo (All are complication cases).

Cases of nasopharyngitis	Vertigo Cured	Improved	Unchanged
Severe	22	10	1
Moderate	8	7	1
Mild	1	2	1
	31	19	4

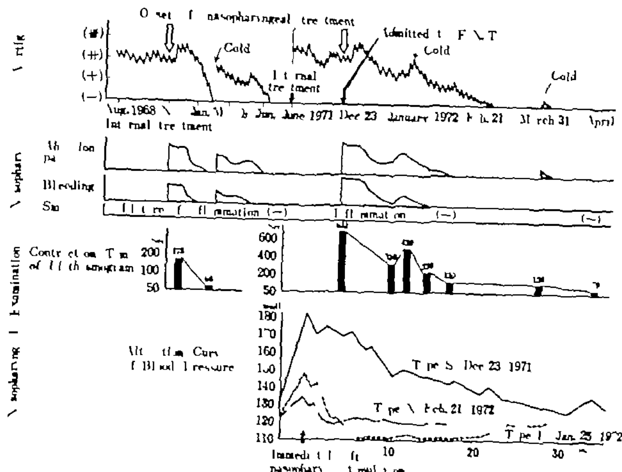


Fig. 61 Case No. 14 36 y.o. F

CP cases 29 normal cases and 2 cases of hyper function Of 35 DP 28 cases were cured (80) 3 cases alleviated and 4 cases unchanged The CP group showed 12 cases of cure (57) and 75° of cure rate was obtained in normal group The rate of cure in the CP group is rather low as compared with that of other groups How ever no cases needed surgical operation because of severe symptoms. In the following a case report of dizziness is described

Case No. 14

A 36 year old house wife w th dizziness.

Chief complaint Rotary vertigo, palpitation and pain in th chest.

History No Specific illness. The symptoms appeared four years ago and were diagnosed as autonomic ataxia" and medication as prescribed fo three months

There was no improvement

She visited an ORL cl ic and minor inflamma tion in th nose was f und but no abnormality was d tected After two months she isited our clinic (3 years and 6 months ago)

Acoustic nerv test was normal, but severe nasopharyngitis was observed. The naso-pharyngeal abrasion was carried out and she once developed intense nflammation but gra dually recovered during t eatment four times a week. Complete cure was achieved after 8 months treatment. She had no relapse for two years since then About one year and six months ago she developed sy ptoms again after ex acerbation of nasopharyngitis. On account of dyspnoe she was admitted to an emergency hospital She was diagnosed as ha ing autonomic ata ia and cardioneurosis For half a year arious treatments were tried but no improvement was mad She visited ou clinic agai and we detected the presence of intense nasopharyngitis.

Clinical finding Th autonomic nerv test was mad by m ans of nasophary geal timulation and a typical autonomic erve disorder was detected Fortunately w had the patient record as shown in F g 61 Tabl 53 and the clinical course of nasopharyngitis corresponded exactly to impro ement of a tonomic nerve disorder

On th 5th day of th t eatment pain in th chest disappeared and on the 10th day no rotary sensation was felt. Th autonomic erv dis order and asopharyng tis showed ma ked

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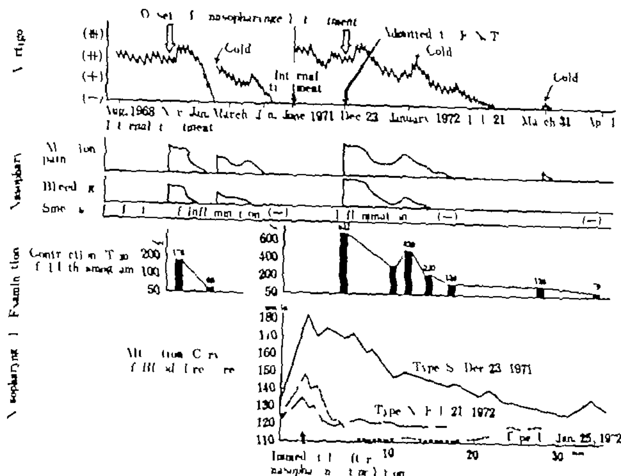


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ment of the symptoms, and in these cases the nasopharyngeal abrasion treatment will produce marked effects.

Case No. 15

An 8 year old school boy with O.D.

Chief complaint Headache

History Frequent headache and chronic repetition of fever. Headache occurs twice or three times a month and the patient tires easily chronic snuffles. O.D was diagnosed at the pediatrician's. Adenoidectomy was performed two years previously but no improvement was achieved. Reasons for visiting pediatric department

1. Always pale and inactive. Frequent visits to the doctor
2. Easily gets tired and soon loses interest in drawing or handicraft lessons.
3. Physically unstable and occasionally shouts with a queer voice.
4. Often uses the word "uninteresting"
5. Easily catches cold and is absent from school with fever of 37 –38 °C

Clinical findings No specific changes in ORL. A nasopharyngeal abrasion caused severe pain which lasted for half a day. Marked post abrasive hemorrhage. The smear specimen disclosed medium scale exfoliation of ciliated epithelium, with swelling of the cytoplasma. A small amount of lymphocytes and pavement epithelium were observed.

Clinical course All medications previously used were discontinued and application of 1% $ZnCl_2$ was exercised daily

1st day Marked abrasion pain and hemorrhage.

10th day Abrasion pain and postabrasive hemorrhage were improved and the patient regained his activity. H used to feel tension in the head although headache was absent, but the sensation of heavy head was much improved. Sniffles remained as usual.

20th day The sensation of heavy head was improved. No more tiredness. He sat at his desk to study of his own accord.

30th day Again caught cold and complained of headache. The nasopharyngeal abrasion caused severe pain and bleeding. (Intense inflammation developed whenever he caught cold.) The author is of the opinion that acute nasopharyngitis with the complication of autonomic nerve disorders should be called a "common cold" The postabrasive pain continued for half a day. Serous rhinorrhea continued half a day. Sniffles increased.

35th day Abrasion pain and bleeding still intense. Headache was present. The usual treatment was continued.

45th day The abrasion pain and bleeding alleviated. The patient said that he felt good. Remission of headache and the heavy feeling were obtained.

50th day A letter from the patient's mother described his marked recovery

80th day Almost no complaint, but it was decided to continue treatment once weekly

Table 56

Case No.	Age	Sex	Symptoms: Major symptom	Symptoms: Minor symptom	Chief complaints	Nasopharynx: Abrasion pain	Nasopharynx: Bleeding	Nasopharynx: Picture of smear preparation	Duration of the treatment	Effectiveness
1	12	♂	ABC	adbef	orthostatic dizziness	#	#	moderate	8 weeks	under observation
2	8	♂	ABD	be	orthostatic dizziness	++	+	—	1 month	cured
3	16	♂	ABE	cfgi	urticaria	++	++	moderate	4 month	cured
4	10	♂	E	abde	slight fever	#	++	moderate	15 days	cured
5	9	♂	BCE	df	headache	++	#	intense	1 month	cured
6	10	♂	BCDE	abde	headache	++	+	moderate	104 days	cured
7	9	♂	ABE	abde	headache	++	+	moderate	125 days	cured
8	8	♂	DE	bce	asthma	++	++	intense	1 year	under observation
9	8	♂	BDE	abe	asthma	+	++	intense	52 days	cured
10	10	♂	DE	bde	rheumatic fever	+	+	moderate	46 days	slightly improved
11	9	♂	B	abdf	rheumatic fever	++	++	moderate	7 weeks	cured
12	16	♀	ABD		rheumatoid arthritis	++	+	intense	68 days	slightly improved
—	—									

Table 55 Duration of reduced amplitude in pulse wa e before and after the treatment of nasopharyngitis and results in dizziness or ertigo.

Duration of reduced mplitude by nasopharyngeal stimulation			Dizziness or vertigo		
Duration of reduced amplitude	Before treatment	After treatment	Cured	Improved	Unchanged
over 501 sec	6 cases (11)	0	3 cases (50°)	3 cases (50%)	0
401 500 sec.	4 (7)	0	1 (25)	2 (50%)	1 cases (25%)
301–400 sec	8 (15)	0	6 (75)	2 (25)	0
201 300 sec.	16 (30°)	2 cases (4 %)	9 (56)	7 (44 %)	0
101 200 sec	11 (20%)	8 (15)	10 (90 %)	1 (10%)	0
1 100 sec	9 (17)	33 (61)	2 (22 %)	4 (44)	3 (34)
below 50 sec.	0	11 (20%)			
Total	54		31 (58)	19 (35)	4 (7)

department or in school health no medical solution has been considered. Orthostatic dysregulation in children occurs with various clinical patterns and cannot be diagnosed by simple criteria It looks like a neurotic disease because of its multiple symptoms In order to provide standard diagnostic criteria, the following criteria are specified

To determine the diagnosis, orthostatic dysregulation should have the following elements

1 Indication of 1 major symptom and 3 minor symptoms
2 Indication of 2 major symptoms and 1 minor symptom
3 Indication of 3 major symptoms

Diagnostic Criteria for Orthostatic Dysregulation

Major symptoms

- A Dizziness or vertigo often occur
- B Uncomfortable feeling when standing In severe cases the patient falls down
- C Uncomfortable sensation while taking a bath or hearing bad news
- D Palpitation or short breathing frequently occur
- E. Difficulty in getting up in the morning and poor condition in the morning

Minor symptoms

- a Palor
- b Poor appetite
- c Occasional abdominal pain
- d Tired feeling or weak feeling
- e Frequent headache
- f *Susceptibility* to vehicle vertigo
- g Decrease of pulse pressure in excess of 16 mmHg by the standing test.
- h. Alteration of systolic blood pressure over 21 mmHg by the standing test
- i Increase of pulse rate over 21 in one minute.
- j Lowering of over 0 2 mV in T I and T II in orthostatic ECG

The so-called orthostatic dizziness or vertigo does not always occur in orthostatic dysregulation It is doubtful whether these symptoms belong to autonomic nerve disorders.

However as explained in the Basic Study of *nasopharyngitis* in relation to extension of contraction time in the pulse wave of the fingertip the orthostatic disorder can be considered to have some relation to nasopharyngitis.

The symptoms of orthostatic dysregulation such as a fainting sensation when standing have close relations with the hypersensitiveness of the autonomic nerves as diagnosed through the pulse wave pattern in the fingertip If we develop this concept we might be able to consider nasopharyngitis as a focus of inflammation which stimulates the autonomic nerves to cause orthostatic dysregulation With this concept we observed the nasopharynx of the school children who had orthostatic dysregulation. Nasopharyngeal observation revealed the presence of intense inflammation (erosion) and local treatment achieved complete cure of the orthostatic symptoms. Adenoidectomy is a useful treatment for orthostatic disorders but the result does not always warrant improve



Fig. 63. Nasopharyngeal smear after the treatment.



Fig. 64. Smear of upper esophagus before the treatment.

pharynx developed medium size flushing and minor tenderness at the right side of the cavity. Adenoidectomy and tonsillectomy were carried out at age of 7. A small amount of pus was detected in the nasopharynx. Microscopic examinations disclosed marked redness all over the cavity which was especially heavy in the dorsal portion of the soft palate extending to the palatine arch. The nasopharyngeal mucous was abraded with cotton applicator. Severe abrasion pain and bleeding were complained of which indicated the presence of intense nasopharyngitis. The smear specimen, showing traces of bleeding, included exfoliation of ciliated epithelium, which was swollen and transformed, and number of wandering leucocytes and lymphocytes were recognized. Infectious bacteria included staphylococcus aureus and other strains. The inflammation was shown to be in highly erosive state.

The upper end of the esophagus was examined with the cotton applicator. Some bleeding and pain were observed. The smear specimen indicated the intense exfoliation of epithelium and wandering leucocytes. Staphylococci aureus were present in the focus of inflammation.

Clinical course. The nasophary ngeal mucosa and the upper end of the esophagus were treated with 1 $ZnCl_2$ every day. The applicator was inserted through the soft palate, especially the

School children are generally susceptible to the common cold and the symptoms are usually severer than those of adults.

The main symptoms of the above cases were the so-called diencephalon syndrome or autonomic dystonia for which no specific methods of treatment have been found It is clinically of interest to observe the cure by means of nasopharyngeal abrasion. The author considers that stimulation of the nasopharynx will relate to the hypothalmus and cause vasomotor contraction or alteration of blood pressure The presence of intense inflammation in the mucus of the nasopharynx is stimulated by the passing of air inhaled from the outside the passing of air always gives stimulations and results in autonomic ataxia O D and diencephalon syndrome If exacerbation of nasopharyngitis is caused by air pollution it is reasonable to consider that a great many autonomic disorders occur due to nasopharyngeal inflammation Table 56 is a consolidated list of 12 cases of O D The significant characteristic of this table is that all cases were treated exclusively by local treatment In the past O D had been considered a difficult disease and no specific treatment except administration of autonomic nerve sedatives has been exercised At least 8 out of 12 cases were cured by means of the nasopharyngeal treatment alone

Orthostatic dysregulation (O D) is not rare in adults In children more cases were found among boys, and in adult cases females of middle age exceeded the males. When females reach the age of menopause their symptoms of O D are confused with menopausal symptoms. The following case is of a middle-aged woman who complained of innumerable symptoms and despite various treatments no results had been achieved

Case No. 16 (Figs. 62–66)

H Y A female 35 years old. Continuous slight fever and neurosis.

Chief complaint Continuous slight fever headache, aching of both sides of the neck, stiff neck, insomnia, lack of appetite gastric ptosis and hypotension.

History She complained of slight fever and headache since three years before and the fever had continued for six months up to the present. (ASL-O and CRP were negative.) Three years previously she had migrane, a pain in the both sides of the neck, a stiff neck and she had been troubled by insomnia and anorexia. After examination by an internist she was diagnosed as having mild gastric ptosis and hypotension (100–65mmHg)

Various medications were tried but in vain symptoms were exacerbated and she was always in bad humor She visited a psychiatrist but no abnormal EEGs were recorded. She visited many doctors but no one diagnosed her illness.

Clinical finding E.N T examinations were normal except for a slight swelling in the nasopharynx. An abrasion with a cotton applicator caused severe abrasion pain in the right side of the nose and bleeding but mild inflammation was noted in the left side of the nose. The naso-

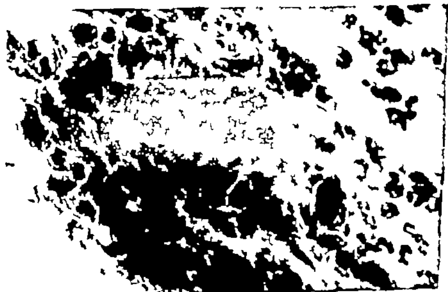


Fig 62. Nasopharyngeal smear before the treatment.



Fig. 63. Nasopharyngeal smear after the treatment.



Fig. 64. Smear of upper esophagus before the treatment.

pharynx developed medium size flushing and minor tenderness at the right side of the cavity. Adenoidectomy and tonsillectomy were carried out at age of 7. A small amount of pus was detected in the nasopharynx. Microscopic examinations disclosed marked redness all over the cavity which was especially heavy in the dorsal portion of the soft palate extending to the palatine arch. The nasopharyngeal mucosa was abraded with cotton applicator. Severe abrasion pain and bleeding were complained of which indicated the presence of intense nasopharyngitis. The smear specimen, showing traces of bleeding, included exfoliation of ciliated epithelium, which was swollen and transformed, and number of wandering leucocytes and lymphocytes were recognized. Infectious bacteria included staphylococcus aureus and other strains. The inflammation was shown to be in highly erosive state.

The upper end of the esophagus was examined with the cotton applicator. Some bleeding and pain were observed. The smear specimen indicated the intense exfoliation of epithelium and wandering leucocytes. Staphylococci aureus were present in the focus of inflammation.

Clinical course. The nasopharyngeal mucosa and the upper end of the esophagus were treated with 1% $ZnCl_2$ every day. The applicator was inserted through the soft palate, especially the



Fig. 65. Smear of upper esophagus after the treatment.

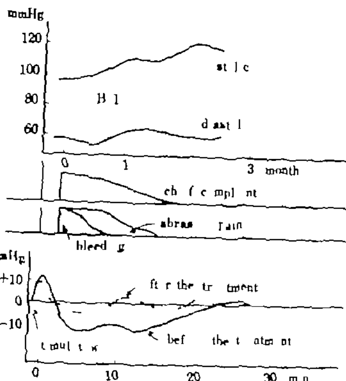


Fig. 66. Case No. 18. E. Y. 32y. o. F.

dorsal portion, and reached the nasopharyngeal cavity. Esophagus insertion was attained passing through the apple shape cavity. The right side wall produced pain and bleeding. The first application of the swab caused pain which lasted for four hours and transient excretion of nasal fluid was observed. The pain was felt at the esophageal wall but no bleeding was observed. The next day she had a good sleep and alleviation of night sweat. The fever began to reduce and on the 15th day it became normal.

She could not believe the recovery since she had been annoyed by persistent fever for three years. After that day she trusted the treatment, and other symptoms which persisted for many years were gradually improved. Abrasion pain and bleeding of the nasopharyngeal cavity were alleviated on the 7th day and bleeding ceased on the 9th day. Abrasion pain disappeared on the 13th day and after the 14th day headache in the right side of the head was completely cured. The nasopharyngeal abrasion reduced the pain

and bleeding after the 15th day of the treatment and the frontal headache (corresponding to the dorsal portion of the soft palate) gradually reduced and finally disappeared on the 16th day of the treatment.

Abrasion of the tonsils produced bleeding, but on the 11th day no bleeding was observed. On the 27th day stiffness of the neck was healed and all of Siebeck's syndrome disappeared. She left the clinic after 44 days of treatment.

She has been visiting this clinic once every week and she has not had the symptoms for two years. The comparison of pre-post treatment is tabulated as follows

	Pretreatment	Posttreatment
Nasopharyngeal abrasion	Marked exfoliation of ciliated epithelium. Presence of large number of lymphocytes and wandering leucocytes.	Normal condition
Plethysmogram of the finger	Contracted for several hours	Normal
Blood pressure curv	P type	N type
Fibrinolysis	331 minutes	161 minutes
Siebeck's symptoms	Night sweat, cold sensation, palpitation, vertigo, headache, constipation and diarrhea	All disappeared

It is interesting to note that alterations of the peripheral pulse wav and blood pressure curv were observed after the stimulation by nasopharyngeal abrasion.

The initial pulse wav showed unlimited contraction (several hours of observing contraction was continued but it did not return to the normal state) but returned to normal after 40 days treatment. The blood pressure alteration pattern was initially of the cholinergic type but was later modified to the N type. Corresponding to normalization of the autonomic disorder symptoms, which were 7 in all, all vanished. Sedation of autonomic disorders may be possible for time with medication, but generally it is impossible to normalize the condition permanently

Discovery of useful treatment for autonomic nerv disorders, which ha been considered subjectiv and psychological phenomena, has endowed the medical world with the possibility of an activ cure by means of local treatment.

W experience many cases like this t the clinic and nearly all the cases gained good results from the nasopharyngeal treatment alone The following is another case with various complaints.

Case No. 17

A.T A 47 year old female complaining of atypical symptoms.

Chief complaints Paroxysmal pain in the postoperativ abdomen. Headache. Stiffness of the neck. Palpitation. Cold sensation of the limbs. Vertigo. Diarrhea and toothache.

History She was hypersensitiv by nature. She was operated on for appendicitis at the age of 33, and thereafter she complained of habitual abdominal pain. Surgical treatments had been made but failed to produce any improvement. Then she developed gastric pain, diarrhea, paraesthesia of the hands and feet associated with palpitation, dizziness, headache, stiffness of the neck, etc. Recently she was diagnosed as having hysteria by neighboring internist. She further developed severe pain in the maxilla (in several teeth and the gums) and the other symptoms were exacerbated.

Clinical findings She had several lesions on the abdomen as result of the surgical treatment, but XP revealed no abnormal picture. N histological changes were apparent in the maxilla but severe inflammation was present in the nasopharynx.

The local treatment produced severe pain and bleeding. The finger pulse w showed a prolonged contraction. The nasopharyngeal treatment was tried and obtained the following results

Clinical course Immediately after the initial treatment, the patient showed systemic hypersensitiveness and had severe toothache. Every portion of the skin was irritable and she complained of tension in the head. She said she was not herself. It seemed as though all symptoms which had previously existed were exacerbated. After the nasopharyngeal treatment she could not mov and had to lay down for two hours. In spite of unfavorable conditions, the treatment was continued. After one month she was rid of the headache, gastric pain, dizziness, cold sensation in both limbs, diarrhea and stiffness of the neck. Continuous treatment produced step by step an improvement and three months later every symptom was cured and disappeared. After tw years she visited the clinic. She was active and cheerful and looked healthy

The case may belong to other territory than autonomic disorders, but, the concept of the nasopharyngeal tretment of autonomic dystonia is applicable.



Fig. 65. Smear of upper esophagus after the treatment.

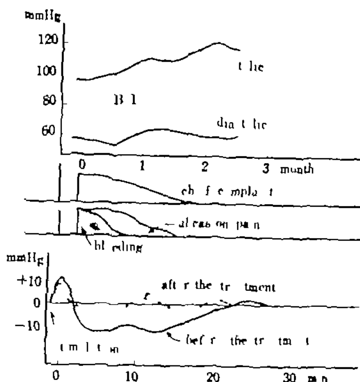


Fig. 66. Case No. 18. E. Y. 32y. o. F

dorsal portion, and reached the nasopharyngeal cavity. Esophagus insertion was attained passing through the appl shape cavity. The right side wall produced pain and bleeding. The first application of the swab caused pain which lasted for four hours and transient excretion of nasal fluid was observed. The pain was felt at the esophageal wall, but no bleeding was observed. The next day she had a good sleep and alleviation of night sweat. The fever began to reduce and on the 15th day it became normal. She could not believe the recovery since she had been annoyed by persistent fever for three years. After that day she trusted the treatment and other symptoms which persisted for many years were gradually improved. Abrasion pain and bleeding of the nasopharyngeal cavity were alleviated on the 7th day and bleeding ceased on the 9th day. Abrasion pain disappeared on the 13th day and after the 14th day headache in the right side of the head was completely cured. The nasopharyngeal abrasion reduced the pain

occasionally dizziness. An internist diagnosed hypotension.

Clinical findings: Blood pressure was 90-60 mmHg. Routine ORL examination revealed no abnormality. Insertion of the cotton applicator into the nasopharynx (passing through the nasal side and from the nasopharynx) and abrasion of the dorsal portion of the upper soft palate provoked severe pain and marked bleeding. She was confirmed as having intense erosive nasopharyngitis. The smear specimen obtained from the swab evidenced marked inflammation. Apparent exfoliation of ciliated epithelium, appearance of wandering leucocytes and proliferation of infectious micro-organisms were detected. The case was confirmed as typical latent nasopharyngitis. Immediately after the local abrasion, the blood pressure pattern showed P type.

Treatment: The cotton applicator dipped into 1% $ZnCl_2$ solution and small amount of Xylocain, was applied to the nasopharynx, particularly to the dorsal portion of the upper palate and all other treatments and medication were discontinued in order to examine the exclusive efficacy of the nasopharyngeal treatment.

On the 10th day of the treatment abnormal feeling of the nasopharynx vanished and the abrasion pain and bleeding gradually alleviated on the 3rd day of the treatment. On the 10th day of the treatment all such symptoms disappeared. Blood pressure was elevated slightly to 100/70mmHg.

On the 20th day the further elevation was achieved and the patient maintained the level (110/70mmHg) (Fig. 67). The examination of the blood pressure curve at this time showed that patient belonged to type N (similar to the pretreatment status).

The nasopharyngeal treatment thus always produces normalization of blood pressure and is applicable to the hypotensive patients. In the hypotensive case, the lowering normalization of blood pressure takes more time as compared with that of diastolic phase (Figs 68, 69). We examined the curve of ambulatory patients (9 cases) which showed that 7 cases responded well to the treatment. Among the treated groups, 2 cases failed to respond to the treatment. They discontinued the treatment after two weeks (Fig 68). It might be that the expected result would have been obtained if they had continued the treatment.

Hypertension

Examination of the nasopharynx of the

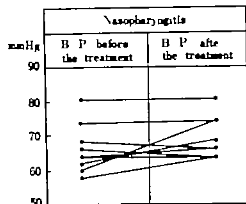


Fig. 68. Improvements of diastolic blood pressure.

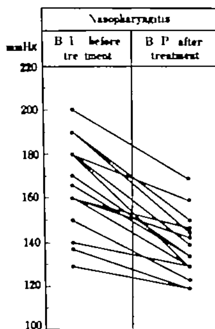


Fig. 69. Improvements of systolic blood pressure.

hypertensive patients always disclosed the presence of severe nasopharyngitis. The continuous local treatment gradually lowered the blood pressure to normal standard as observed in the hypertensive cases. In the hypertensive cases blood pressure types of NSBP as shown in the hypotensive cases, belonged mostly to S or P type, but they changes to N type when they responded to the nasopharyngeal treatment. The clinical courses of both cases resemble each other and in this respect the author considered hypertension and hypotension belong to the same category of disease. We examined the

Table 57 Pathological alteration of the blood pressure.

Case No.	Age	Sex	NSBP Type	B.P before and after the treatment		Duration of treatment
				before	after	
1	30	♀	S	96/66 mmHg	118/64 mmHg	6 months
2	41	♀	P	96/64	116/66	3 months
3	38	♂	S	108/74	unchanged	2 weeks
4	70	♂	P	96/58	120/64	3 months
5	21	♀	S	100/64	114/64	3 months
6	60	♀	N	110/80	unchanged	2 weeks
7	28	♂	N	108/68	114/66	1 month
8	36	♀	P	100/62	114/68	4 months
9	32	♀	P	90/60	110/74	3 weeks

3) Nasopharyngeal Treatment and Changes in the Blood Pressure Curve

Nasopharyngela treatment produced immediate and apparent changes of blood pressure. As the reason for hypertension or hypotension in the presence of an intense inflammation in the nasopharyngeal cavity it may be considered that stimulative air always passes through the nasal cavities giving constant stimulation to the mucosa of the nose and the constant stimulation produces elevation or lowering of blood pressure.

A primary consideration was that after stimulation of the nasopharynx blood pressure type P (lowering type) might have caused hypotension and the type S (elevating type) for hypertension. Actual examination disclosed that this pattern was not true

Nevertheless, there were not many N types and most of them belonged to either S or P which were related to autonomic imbalance The local treatment of nasopharyngitis reduced hypertension and elevated blood pressure in hypotensive patients. In the following the author describes the cases of hypotension and hypertension separately

Hypotension

Hypotension is frequently complicated by autonomic disorders and patients frequently complain of symptoms such as gastroptosis orthostatic vertigo and tiredness. Hypotension is often observed in middle aged women and often causes confusion of diagnosis with menopausal disorders. In short hypotension is a unknown etiology without any effective treatment. Many hypotensive patients, because of scarcity of symptoms, have been left untreated The author investigated the hypotensive cases in relation to neurotic complications. Examination of the nasopharynx showed that without exception they had inflammation of the nasopharynx. As usual the nasopharyngeal treatment was applied. Amazing enough all cases, more or less produced elevation of blood pressure.

Case No. 18 (Fig 67)

E.Y 32 year old female with hypotension (essential)

Chief complaint Stiff neck, abnormal feeling of the nasopharynx, vertigo, gastric ptosis.

History She complained of abnormal feeling since the seven years previously She also complained of stiff neck, slight gastric ptosis and

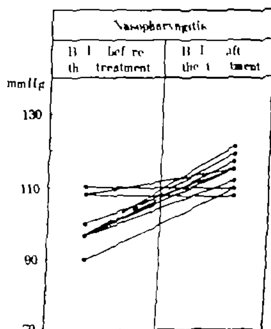


Fig. 67 Improvements of systolic blood pressure.

That is, cotton applicator dipped in 1% $ZnCl_2$ was inserted into the dorsal portion of the upper soft palate through the nasopharynx arch. The clinical course is demonstrated in Fig. 72. It is worth nothing that the clinical course of the improvement in blood pressure corresponded to the improvement of nasopharyngitis.

As indicated in the diagram, the duration of observation was 7 months. The patient visited the clinic once or twice annually to measure the blood pressure. After complete normalization, exacerbation of nasopharyngitis was not associated with an elevation of the blood pressure. However it is hoped that the hypertensive patient will consult the doctor at an early stage of the disease for nasopharyngeal treatment.

As the author felt it was interesting another case is described below

Case No. 20 (Fig. 73)

M.W. A 30 year old female with essential hypertension.

Chief complaint Headache. Hypertension.

History She had complained of headache, nasal congestion and rhinorrhea since she was 17 years old.

About 6 years ago she got hypertensive during her first pregnancy (170–120mmHg). After the child birth blood pressure returned to normal. When she was pregnant three years ago, her blood pressure began to rise in the 7th month of pregnancy and the condition never improved after the childbirth. Hypotensives were prescribed but with no effect. Exacerbation of headache and nasal congestion made her to come to our clinic.

Clinical findings Blood pressure 170–120 mmHg. No protein was found in urine. Examination of internal medicine did not show any abnormality. Routine ORL showed that she had slight hypertrophy in the inferior turbinate body and slightly serious rhinorrhea. No other changes were observed. The nasopharyngeal abrasion test disclosed a severe pain and bleeding as indication of an intense inflammation. The smear specimen indicated the presence of intense cross inflammation in the nasopharynx, with the appearance of number of wandering leucocytes, proliferation of bacteria and exfoliation and transformation of ciliated epithelium. NSBP was S.

Clinical course: Administration of hypotensive drugs was discontinued except the local application with 1% $ZnCl_2$ solution (with small amount of anaesthetic added). The improvement is shown in Fig. 74. The initial hypertensive value, 170–120mmHg, returned to 148–114mmHg and on the 10th day of the treatment the improvement reached 148–110mmHg. On the 20th day all other symptoms, headache, nasal congestion and rhinorrhea disappeared. (Hypertensive patients used to complain of headache and stiff neck. In the past these symptoms had been considered to be due to hypertension. The author postulates these symptoms might be derived from nasopharyngitis or the presence of inflammation at the upper end of the esophagus and the pain might be the dispersion of these inflammations.)

The postabrasive bleeding vanished on the 10th day and the smears became normal on the 25th day. The exfoliation of ciliated epithelium was reduced. The wandering leucocytes and infectious micro-organisms were almost absent from the site. On the 40th day the systolic blood pressure reached 130–98mmHg, which was 20mmHg lower than the initial value. The treatment was discontinued but the measurement of blood pressure always indicated 130–100mmHg. The NSBP pattern indicated N type after the treatment.

T ble 58 Cases of Hypotension Type changes of NSBP before and after treatment.

Type of NSBP (Nasopharynx stimulation blood pressure)	Treatment of nasopharyngitis	
	before	fter
S Type	3 (33)	1 (11)
P Type	4 (44)	1 (11)
N Type	2 (23)	7 (78*)

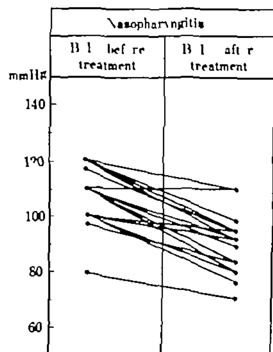


Fig 70. Improvements of diastolic blood pressure

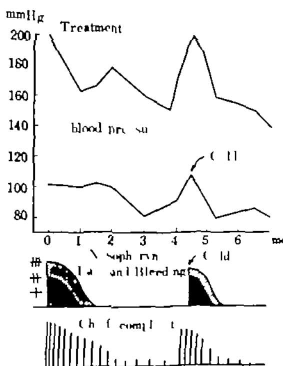


Fig 71 Case No. 19 Hypertension(F.M 54 y o. F)

curve of 15 patients of hypertension which showed that all cases responed well to the treatment (Figs. 69 70)

Case No 19 (Fig 71)

F M. A 54 year old female with essential hyper tension.

History She caught cold three years ago. Since that time she felt abnormality in the throat. She was diagnosed as having hypertension and various treatments were tried but in vain. She feared that she had cancer of the nasopharynx and visited our clinic.

She had 200mmHg of systolic pressure and 100mmHg of diastolic. She complained that the increase of abnormal feeling seemed to correspond to an elevation of blood pressure.

Clinical findings A physical examination disclosed that she had renal and hepatic impair ment. XP of the heart indicated hypertrophy of the left ventricle but the symptom was not severe. She was diagnosed as having essential hypertension. Routine ENT examination failed to detect any abnormality but the nasopharyngeal abrasion test disclosed a marked inflamma tion in the nasopharynx. She complained of intense abrasion pain and bleeding The smears showed marked exfoliation and transformation of ciliated epithelium and proliferation of micro-organisms.

Clinical course All other medications and treatment were discontinued except application of the cotton applicator to the local inflammation.

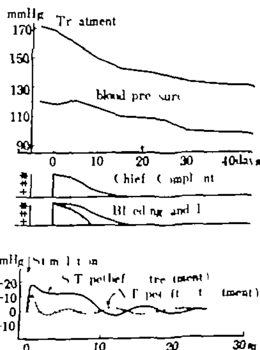


Fig. 72. Case No. 20 (M.W 30 y o. F)
Diagram of Clinical Course.

Table 60 Cases of frontal pain (17cases).

No.	Age	Sex	Onset of illness	Grade	Time/day	Remarks
1	37	♀	2 months ago	moderate	occasionally	
2	55	♂	1 month	moderate	continuously	
3	28	♀	2 weeks	light	continuously	
4	39	♀	2 weeks	light	continuously	
5	36	♀	10 years	moderate	after reading	sinusitis (+)
6	26	♀	1 year	light	during the work	tonsillectomy (15 yrs. old)
7	21	♂	1 month	light	continuous	headache after tonsillectomy
8	22	♂	2 3 months	light	continuous	
9	60	♀	6 months	moderate	continuous	
10	21	♂	3 weeks	moderate	continuous	headache after cold
11	19	♂	2 3 years	severe	continuous	
12	24	♂	4 years	severe	afternoon～night	
13	52	♀	9 months	severe	continuous	
14	17	♂	3 months	moderate	continuous	
15	34	♂	3 months	moderate	continuous	nasal allergy (+)
16	25	♂	2 years	moderate	continuous	
17	26	♂	12 3 years	moderate	continuous	tonsillectomy (16 yrs. old) septal plastic (23 old)

History An intense headache in the forehead had occurred since four years previously was especially severe during the afternoon and evening. Sleep was disturbed and the patient was admitted to psychiatry department for the treatment of insomnia. In spite of two years of treatment no effect was obtained. Because of nasal congestion and rhinorrhea, the patient visited our clinic.

Clinical observation A little nasal fluid was observed in the nasopharyngeal cavity but there were no abnormal findings. X-ray showed no changes in the paranasal sinus, and the throat culture showed no existence of pus. Sinusitis was denied. Insertion of the cotton applicator through the nasopharynx produced severe abrasion pain and bleeding. A severe inflammation was recognized at the dorsal portion of the soft palate. When the swab passed through the nasopharyngeal portion severe pain eradiated to the forehead.

Note The author found that anaesthesia of the dorsal portion of the soft palate occasionally reduced pain in the head, but many years passed before he realized the relationship between headache and nasopharyngitis.

Clinical course The day after the treatment the patient showed good response to the treatment and alleviation of the pain was attained. He used to use sleep inducing drugs because of fear of insomnia. On the 25th day of the treatment he was able to terminate the use of the drug. A headache was felt in the afternoon.

The symptom completely disappeared on the last day. When he travelled by train headache again occurred. Abrasion pain returned, but after week of the treatment the abrasion pain disappeared and the symptom was also cured.

The treatment was continued for two months and perfect cure was attained. There are a great number of similar cases but they responded well to the treatment. Duration of the symptom varies, some within three weeks while others had persistent headache for over 10 years. In any case the local abrasion treatment cured them perfectly.

Most patients complained of dizziness while they were in a crowd. This is considered to be the result of stimulation by dust affecting the

Table 61 Relation between the grade of headache and nasopharyngeal lesions.

No.	Grade	Nasopharyngeal base	
		Abrasion pain	Bleeding
1	moderate	+	±
2	moderate	+	−
3	light	+	−
4	light	++	−
5	moderate	++	+
6	light	+	−
7	light	+	−
8	light	+	−
9	moderate	++	+
10	moderate	++	+
11	severe	+	+
12	severe	++	++
13	severe	+	−
14	light	+	+
15	light	+	±
16	light	+	−
17	light	+	+

4 Relation between Nasopharyngitis and Pain in the Head and Neck Region

Nasopharyngitis in most cases is latent and the patients do not complain of local symptoms, but it often produces pain No one has ever considered participation of nasopharyngitis when the patient has a pain or unusual sensory disorders of unknown etiology This is because the existence of nasopharyngitis has been completely ignored by the medical profession but the treatment of this disease has improve dvariuos diseases of unknown origin

The major categories of pain are included in the following list

1 Headache
2 Stiff neck
3 Cervical pain
4 Abnormal sensation in the throat
5 Toothache and gum pain

Other pains are neuralgia rheumatism and gout which can be cured by nasopharyngeal treatment

1) Headache

Headache is still unknown as to its mechanism and etiology HOC Committee of N I H

Table 59 Classification of headache

1	headache of migraine type
	A. classic migraine
	B. common migraine
	C cluster migraine
	D hemiplegic and ophthalmologic migraine
	E. lower half" headache
2	muscle contraction headache
3.	combined headache vascular and muscle contraction
4	headache of nasal vasomotor reaction
5	headache of delusional, conversion or hypochondrial states
6	non-migrainous vascular headaches
7	traction headache
8.	headache due to cranial inflammation
9	13 headaches due to diseases of ocular aural, nasal and sinus dental or other cranial or neck structures
14	cranial neuritides
15.	cranial neuralgias

classified the headache as shown in Table 59

There are various classifications, but vasomotor and contraction headache is associated with the severest pain. Clinically headache is classified as familial headache, adenoide headache or Thornwaldt's headache and so on. *Since the old days* many clinicians have ideas concerning the etiology but none with persuasive *data*

Headache as examined from the aspect of nasopharyngeal inflammation may give an advangageous solution The author may say headache is a referred pain originating at the nasopharyngeal site Headache as classified *according* to the site of onset can be listed as *frontal* pain temporal pain parietal pain and occipital pain. There exist inflammation sites corresponding to the site of headache and the treatment of the inflammation can cure headache with 100 % effectiveness. A simple anesthetic treatment of inflammation site produced an analgesic effect though transient The corresponding points are illustrated below (Fig 78)

Frontal	Dorsal portion of the soft palate occasionally agger nasi
Occipital portion	Dorsal cavity of the nasopharynx (Adenoids)
Temporal	Dorsal half of the inferior nasal meatus, the left or right side
Parietal	Upper portion of the nasopharyngeal cavity

A greater number of headaches of unknown origin can be treated by the local abrasion of the corresponding site of an inflammation except when the cause is clearly confirmed

Frontal Pain

Case No. 21

A 24 year old male Frontal headache

Table 64 Cases of the temporal pain.

No.	Age	Sex	Onset of illness	Grade	Time/day	Side wall of the inferior meatus: Abrasion	Side wall of the inferior meatus: Bleeding	Duration of treatment	Effect
24	52	♀	2 eeks before	light	continuous	+	−	5 days	cured
25	40	♂	7 years	severe	turning points of the seasons	++	+	5 days	cured
26	19	♀	5-6 years	moderate	afternoon~ evening	++	++	3 weeks	cured
27	36	♀	2 years	moderate	2 3 hours	+	+	2 weeks	cured
28	23	♂	4 5 years	severe	morning	++	+	20 days	cured
29	25	♂	10 day	moderate	continuous	++	+	3 days	cured
30	45	♀	6 months	moderate	continuous	++	++	2 weeks	cured

neck pain eradiates to the occipital portion. He sited an internist and orthopedic surgeon but no abnormality was diagnosed. No nasal symptom was observed.

Clinical findings The nasal mucosa showed slight redness but there were no adenoids and no abnormal findings in the dorsal portion of the nasopharynx. An abrasion of the nasopharyngeal site produced severe pain and bleeding. The patient explained that the pain was like thrusting to the occipital portion of the head. The abrasion test indicated no severe inflammation.

Clinical course For the first ten day the abrasion pain and bleeding were severe and no alleviation of the pain was attained. On the 15th day the abrasion pain and bleeding abated and on the 20th day all the symptoms disappeared. Since then no recurrence was reported.

T ble 63 shows six randomly selected cases. In contrast to the above case, they responded well to the treatment and the cure was achieved in a comparatively short period Relation of occipital pain and inflammation of the dorsal portion of the nasopharyngeal ca ity has been explained frequently Adenoids and Thornwaldt headache were described by the i estigators in the past Headache originating from the adenoids was improved by adenoidectomy Headache of adenoid origin often occurs in the occipital portion, but not alway so Adenoidectomy can cure nflammation t the dorsal portion of the nasopharynx but abrasion t the time of operation or local anaesthesia may cure nasopharyngitis. Thornwaldt headache is observed in the occipital portion only Bursa pharyngae may exist in he dorsal portion of the nasopharynx and the induction of pain is called "Thornwaldt headache" However the lack of Bursa may also cause occipital pain as a pattern of nasopharyngitis.

The uthor intentionally selected two cases here because he considers it might be unaccepta ble to postulate symmetric relationship between inflammation and pain. The finding was obtained finally after a search for the cause of pain. Considering the correlation existing in occipital headache, the author at first considered inflammation t the side wall of the nasopharynx, but later it was found that inflam.

Table 65 Cases relieved within three weeks (24 cases)

Case No	Localization	Degree	Duration of treatment
1	frontal		12 days
2	frontal		10 days
3	frontal		5 days
4	frontal		4 days
5	frontal		1 wk
7	frontal		1 k
8			13 days
10			3 days
14			2 wk
15			10 days
18			15 days
19	occipital		1 k
20	occipital		3 k
21	occipital		2 wk
23	occipital		3 wk
24	temporal)		5 days
25	temporal 1)	++	5 days
26	temporal 1)		3 wk
27	temporal 1)		2 k
28	temporal( )		20 days
29	temporal(l)		3 days
30	temporal( )		2 k
31	not localized		17 days
32	not localized		2 wk

Table 62 Relation between the onset nd grade of headache and the duration of the treatment.

No.	Onset of 'Ilness	Grade	Duration of treatment	Effectiveness
1	2 months ago	moderate	12 days	cured
2	1 month	moderate	10 days	cured
3	2 weeks	l ght	5 day	cured
4	2 weeks	light	4 days	cured
5	10 years	moderate	1 week	cured
6	1 year	light	1 month	cured
7	1 month	light	1 week	cured
8	2 3 months	light	13 days	cured
9	6 months	moderate	4 weeks	cured
10	3 weeks	moderate	3 days	cured
11	2 3 years	severe	about 2 months	improved
12	4 years	severe	about 4 months	cured
13	9 months	severe	bout 3 months	cured
14	3 months	moderat	2 weeks	cured
15	3 onths	moderate	10 days	cured
16	2 years	moderate	1 month	cued
17	1 3 years	moderate	1 month	cured

autonomic nerve reflex or changes of vasomotor activity in the cranium (Refer to dizziness and nasopharyngitis.) Headaches of hyper tensive patients are not always related to the elevated blood pressure Exacerbation of nasopharyngitis may explain the reason Table 60 demonstrates the results of the treatment in 17 randomly selected cases who complained of forehead pain which was cured by means of the nasopharyngeal treatment but no medication was exercised. The table includes 4 cases of sinusitis. As sinusitis is considered a cause of headache the author tried to eliminate the case Sinusitis may become an indirect cause but the author has to examine more cases before he decides the causal relationship Table 61 shows a comparison of the grade of pain and the degree of inflammation (according to the severity of abrasion pain) All cases had moderate to severe nasopharyngitis and the degree of the headache ran parallel to the severity of the inflammation As shown in Table 62 the length of the treatment and the alleviation of the headache does not associate each other Case No 5 was cured of the headache, which had persisted for over 10 years, in one week, while No 12 had to take four months treatment to attain complete cure In general most patients responded to the treatment in two or three weeks and complete cure was attained within the period

Occipital Pain

Case No 2?

A 27 year old male with occipital pain.

History He complained of dryness of the nose without any reason since four or five years previously Occipital pain developed especially severe when he bent over When he picked the

Tabl 63 Case of occipital pain (6 cases)

No.	Age	Sex	Onset of illness	Grade	Time/day	Dorsal wall of nasopharynx: Abrasion	Dorsal wall of nasopharynx: Bleeding	Duration of treatment	Effect
18	27	♂	6 months before	moderat	occasionally	++	+	13 day	cured
19	22	♂	1 month	moderate	conti uous	++	++	1 week	cured
20	28	♂	4 weeks	moderat	night~morning	+	++	3 weeks	cured
21	20	♂	10 months	light	occasionally	+	−	2 weeks	cured
22	66	♀	6 onths	severe	continuous	+++	++	4 weeks	cured
23	27	♂	4–5 y ars	severe	continuous	+++	++	5 weeks	cured

Table 64 Cases of the temporal pain.

No.	Age	Sex	Onset of illness	Grade	Time/day	Side wall of the inferior meatus		Duration of treatment	Effect
						Abrasion	Bleeding		
24	52	♀	2 weeks before	light	continuous	+	−	5 days	cured
25	40	♂	7 years	severe	turning points of the seasons	++	++	5 days	cured
26	19	♀	5–6 years	moderate	afternoon~evening	++	++	3 weeks	cured
27	36	♀	2 years	moderate	2 3 hours	+	+	2 weeks	cured
28	25	♂	4 5 years	severe	morning	+	+	20 days	cured
29	23	♂	10 day	moderate	continuous	++	+	3 days	cured
30	43	♀	6 months	moderate	continuous	++	++	2 weeks	cured

neck pain eradiates to the occipital portion. He visited an Internist and orthopedic surgeon but no abnormality was diagnosed. No nasal symptom was observed.

Clinical findings The nasal mucosa showed slight redness but there were no adenoids and no abnormal findings in the dorsal portion of the nasopharynx. An abrasion of the nasopharyngeal site produced severe pain and bleeding. The patient explained that the pain was like thrusting to the occipital portion of the head. The abrasion test indicated no severe inflammation.

Clinical course For the first ten day the abrasion pain and bleeding were severe and no alleviation of the pain was attained. On the 15th day the abrasion pain and bleeding abated and on the 20th day all the symptoms disappeared. Since then no recurrence was reported.

Table 63 show six randomly selected cases. In contrast to the above case, they responded well to the treatment and the cure was achieved in a comparatively short period Relation of occipital pain and inflammation of the dorsal portion of the nasopharyngeal ca ty has been explained frequently Adenoids and Thornwaldt headache were described by the investigators in the past. Headache originating from the adenoids was improved by adenoidectomy Headache of adenoid origin often occurs in the occipital portion, but not al y so Adenoidectomy can cure inflammation at the dorsal portion of the nasopharynx but abrasion t the time of operation or local anaethesia may cure nasopharyngitis. Thornwaldt headache is bserved in the occipital portion only Bursa pharyngae may exist in the dorsal portion of the nasopharynx and the induction of pain is called "Thornwaldt headache" However the lack of Bursa may also cause occipital pain as a pattern of nasopharyngitis.

The uthor intentionally selected two cases here because he considers t might be unacceptable to postulate symmetric relationship between inflammation and pain. The finding was obtained finally after a search for the cause of pain. Considering the correlation existing in occipital headache the uthor at first considered inflammation t the side wall of the nasopharynx, but later it was found that inflam-

Table 65 Cases relieved within three weeks (24 cases)

Case No	Localization	Degree	Duration of treatment
1			12 days
2			10 days
3			5 days
4			4 days
5			1 wk
7	frontal		1 wk
8			13 days
10			3 days
14			2 k
15			10 day
18			15 day
19			1 wk
20	occipital		3 wk
21			2 k
23			3 wk
24	temporal( )		5 days
25			5 days
26	temporal(l)		3 wk
27			2 k
28	temporal( )		20 days
29	temporal(l)		3 days
30	temporal( )		2 wk
31	not localized		17 day
32	not localized		2 wk

Table 66 Cases relieved in bout one month
(5 cases)

Case No.	Localization	Degree	Duration of treatment
6	frontal		1 mo
9	frontal		4 wk
16	frontal		1 mo
17	frontal	•	1 mo
22	occipital		4 wk

T bl 67 Cases relieved over one month (3 cases)

Case No.	Locali-zation	De-gree	Duration of treatment	Remarks
11	frotal		ca. 2 mo	w th a sl ght neurosis
12	frotal	•	ca. 4 mo.	anamnetic neurasthenia
13	frotal		ca. 3 mo.	atta ked by nfluenza dur g treatment

slight moderate severe

mation at the site had caused otalgia The causation of pain at the temporal was found to respond after moving the probe forward, i e. to the side wall of the meatus nasi inferior The symmetric relation was quite close and all cases attained cure within a short period (Table 31) In some cases the opening of the meatus nasi inferior was insufficient and insertion of the cotton applicator was difficult. The inferior nasal concha must be treated surgically to enable sufficient application of the local treat ment The symmetric relationships of head ache and the site of nasopharyngeal inflam mation are described and the number of days required for complete cure are tabulated in Tables 65 66 and 67

As shown, 74 of cure (24 out of 32) was attained within three weeks and 15° in one month but there were only 3 cases that took over one month for treatment. The above 32 cases are unrelated to sinusitis, which has been considered an important causal factor of head-ache. Deformity of the septum was also considered to cause headache but we did not give special consideration to the treatment of the deformity and local abrasion was carried out.

Temporal pain

The temporal pain has more clear cut cor respondence with inflammation because of the locality If the pain occurs to the left side the inflammation is found in the left upper portion of the meatus nasi inferior and does not cor respond to inflammation existing in any other site. Inflammation at the corresponding site will have a severe abrasion pain and bleeding The smears reveal inflammation at the site. We often observe disappearance of pain after simple application of local anaesthesia (Table 64)

Case No. 23 (Fig 73)

S.K. A 25 year old male w th pain in the tempo-ral region.

History Th patient had severe pain in the right side of the head without any apparent cause. The stinging pain was almost ntolera-ble. An oculist discovered impairment of vision and rectifying eyeglasses were prescribed but in vain. Later he had sl ght nasal conges-tion and visited an ORL clinic for the treatment of sinusitis but no mprovement was achieved. Then he visited our clinic

Clinical observations Sl ght deformity of the septum was observed in the right nose. The nasal mucosa was faintly red, but no bnormality

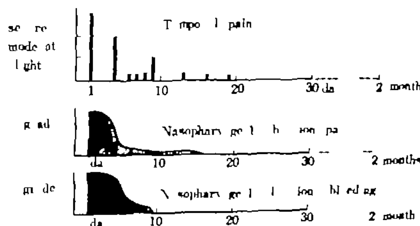


Fig. 73. Case No. 23 (S.K. 25 y o. M.) Case of the right temporal pain.

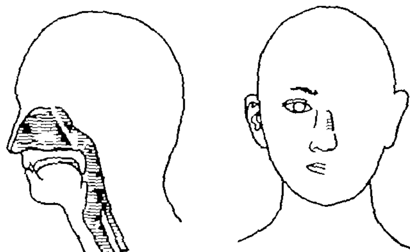


Fig. 74. Radiated headache.

was observed in the meatus. X-ray and probing examination denied sinusitis. The right meatus nasi inferior was rubbed with cotton swab along the upper portion, and intense pain and bleeding were observed. The smears revealed marked inflammation after the culture.
The usual treatment with 1% $ZnCl_2$ relieved the pain. 2% xylocain and 1% $ZnCl_2$ were used for the treatment and other medication was discontinued.
Clinical course was indicated in Fig. 73.
As shown, severe pain disappeared on the day after the treatment and the patient drunk to the bottom next day.
The pain recurred after four days and the continuous treatment completely cured the migrain. The bleeding which had been observed until the 5th day of the treatment discontinued thereafter.

Case No. 21

K.U. A 9 year old girl with temporal pain.
History The pain had been persisten for four to 8 years. When she was tired pain was severe. She was given analgesics. An internist and orthopedic surgeon discovered no abnormality. Familial headache was recorded.
Clinical observations Routine ENT examination disclosed no abnormality. A slight rash and abrasion pain were recognized, but severe abrasion pain was was complained of at the left meatus nasi inferior.
With the passing of the swab she complained of severe pain which radiated towards the left side head. Marked bleeding at the site was noted.
Clinical course Treatment with 1% $ZnCl_2$ (for the first one or two days xylocain was previously applied) was employed. No improvement was obtained on the day after the treatment. On the 3rd day of the treatment headache subsided, and gradually disappeared. No analgesics were used on the 10th day of the treatment. Three weeks of treatment cured her headache. The abrasion pain and bleeding disappeared on the 7th day of the treatment.

2) Pain other than Headache

Pains occur in the face, shoulder, neck and ear. The author sought for the original sites of inflammation and the referred pain, and obtained following symmetric correlations.

Pain in the neck (unusual sensation) ↔ *Palatine tonsil (chronic tonsillitis)*
Otalgia ↔ Pharyngeal orifice of auditory tube
Stiff neck ↔ Upper part of the esophagus
Facial pain ↔ Base of the nasal cavities

3) Paraesthesia in the Lateral Neck

Pain or hyperesthesia in the lateral neck is often explained in relation to stimulation or dislocation of the cervical vertebra, or by the term "cervical syndrome". The author has no sufficient data for the hypothesis, but, he considers it is worth taking into account the participation of chronic tonsillitis. The author has discussed the methods to confirm the presence of inflammation which caused headache.

1. The smear specimen (to examine exfoliation of epithelial cells, wandering cells and proliferation of micro-organisms)
2. Abrasion pain
3. Postabrasive hemorrhage

Table 66 Cases relieved in about one month (5 cases)

Case No.	Localization	Degree	Duration of treatment
6	frontal		1 mo
9	frontal	*	4 wk
10	frontal	*	1 mo
17	frontal	*	1 mo
22	occipital		4 wk

Table 67 Cases relieved over one month (3 cases)

Case No.	Localization	Degree	Duration of treatment	Remarks
11	frontal	*	ca. 2 mo.	with a light neurosis
12	frontal		ca. 4 mo.	anamnestic neurasthenia
15	frontal	**	ca. 3 mo.	attacked by influenza during treatment

slight moderate severe

mation at the site had caused otalgia The causation of pain at the temporal was found to respond after moving the probe forward i e to the side wall of the meatus nasi inferior The symmetric relation was quite close and all cases attained cure within a short period (Table 31) In some cases the opening of the meatus nasi inferior was insufficient and insertion of the cotton applicator was difficult The inferior nasal concha must be treated surgically to enable sufficient application of the local treatment The symmetric relationships of headache and the site of nasopharyngeal inflammation are described and the number of days required for complete cure are tabulated in Tables 65 66 and 67

As shown 74% of cure (24 out of 32) was attained within three weeks and 15% in one month but there were only 3 cases that took over one month for treatment. The above 32 cases are unrelated to sinusitis, which has been considered an important causal factor of headache Deformity of the septum was also considered to cause headache but we did not give special consideration to the treatment of the deformity and local abrasion was carried out

Temporal pain

The temporal pain has more clear cut correspondence with inflammation because of the locality If the pain occurs to the left side the inflammation is found in the left upper portion of the meatus nasi inferior and does not correspond to inflammation existing in any other site Inflammation at the corresponding site will have a severe abrasion pain and bleeding The smears reveal inflammation at the site We often observe disappearance of pain after simple application of local anaesthesia (Table 64)

Case No 23 (Fig 75)

S.K. A 25 year old male with pain in the temporal region

History The patient had severe pain in the right side of the head without any apparent cause. The stinging pain was almost intolerable. An oculist discovered impairment of vision and rectifying eyeglasses were prescribed but in vain. Later he had slight nasal congestion and visited an ORL clinic for the treatment of sinusitis but no improvement was achieved. Then he visited our clinic.

Clinical observations Slight deformity of the septum was observed in the right nose The nasal mucosa was faintly red, but no abnormality

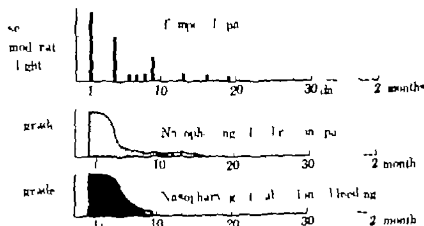


Fig. 75. Case No. 23 (S.K. 25 y o. M) Case of the right temporal pain.

and needed daily massage. She was told that she had intense stiffness in the neck. (Stiffness observed is caused by esophagitis and the improvement of the disease immediately relieves the patient of the stiff neck.) An internist and gynecologist diagnosed climacteric disturbances. Hormone treatment was prescribed but produced no effects. The patient had nasopharyngitis but was free from any other disorders. Unusual feeling of the esophagus was absent and no abnormalities were found in the cervical vertebrae.

Clinical findings Insertion of pharyngeal swabs to the esophagus produced sharp pain, especially the right wall which was symmetric to the site of stiff neck. The sharp pain produced by the swab abrasion passed through to the right side of the neck.

Post abrasion hemorrhage was observed and the symptom suggested cancer at the entrance of the esophagus. Epithelial cells in the smears were inspected microscopically and marked inflammation was detected by the presence of large number of neutrophilic leucocytes, wandering cells, exfoliation of deformed epithelial cells and proliferation of bacteria. However no cancer cells were observed.

Clinical course The local treatment was carried out while preparing the tissue section for pathological examination.

The treatment was carried out with 1 $ZnCl_2$ solution every day. Rapid improvement was obtained and on the 5th day of treatment almost no bleeding was observed. On the 11th day abrasion pain was gone and the stiff neck was completely healed.

About 6 months later she caught cold and developed stiff neck in the left side. The esophageal abrasion caused marked bleeding. The usual treatment attained the disappearance of the stiffness in one week and no complaint has been heard from her since.

Localized esophagitis has been reported as a cause of esophageal neurosis but no reports have been published on stiff neck. Several reports on diagnosis of esophagitis did not describe precise clinical observations on esophageal changes, since no abrasion preparations were examined. Boyo investigated the relations between abrasion preparations and localized esophagitis.

Stiff neck is explained in relation to cervical syndrome. The cause of syndrome is ascribed to dislocation of cervical vertebrae but the author considers esophageal inspection should be carried out first. Certain cases of clinically confirmed dislocation of cervical vertebra did not respond to stretch treatment but were successfully cured by the local abrasion treatment. Several cases with tangled relations were observed. A symmetric inflammation of the esophagus related to chronic tonsillitis, and the inflammation further influences the localized nasopharyngitis, which is derived from deformed nasal septum. (Reference is made to the Basic Study on symmetric relationships between inflammation and ORL disorders.)

6) Facial Pain (Trigeminal Neuralgia)

The term "trigeminal neuralgia" implies an anatomical relation to the trigeminus nerve reflex, but clinically it is not always so. The author tried to locate the site of inflammation of the nasal mucosa corresponding to the pain spot in the face, and found the inflammation at the agger nasi, meatus nasi medius and the base of the nasal cavities. (Inflammation is meant to be the site of lesion only confirmed by swab abrasion and the severity is judged by the degree of bleeding and abrasion pain.)

Case No. 26

H.S. A 20 year old girl with facial pain.

History About month before the patient felt pricking pain in the right cheek extending to the whole face. Also headache in the right forehead. Since then the pain was induced whenever she inhaled cool air, became tired or while she was in an irritable condition, but did not occur while in warm room. (It was winter when she visited our clinic.) When the pain was severe nausea and vomiting attacked her. She occasionally complained of right otalgia. About 15 days before she had been admitted to the hospital and diagnosed as having trigeminal neuralgia, but no treatment alleviated the pain.

Clinical observations No abnormal changes were observed in the facial nerves. Blood and urine were normal. Pain was located at the right superior and inferior orbital foramen and at the root of the zygomatical arch. For 15 days internal medicine failed to produce any result and the patient was transferred to the ENT department.

No abnormality was obtained by routine ENT examinations.

Abrasion of the nasopharynx produced sharp pain which lasted for 3 hours with vomiting and nausea. However the pain at the right cheek and aural pain completely disappeared.

The treatment was continued to the next day but other medication was discontinued. The abrasion pain subsided and no bleeding was observed.

On the 5th day of treatment the abrasion pain

Also the author explained correlations between the smear preparation and the clinical pictures, such as abrasion pain and bleeding and a physician may confirm the progress of inflammation from observation of the smears. Diagnostic criteria for chronic tonsillitis are based usually on gross examinations, such as unclear lacunae, outlook, submerged tonsil and other changes that are visible to the eyes. The postoperative examinations often disclose intensive inflammation. Clinically chronic tonsillitis is frequently associated with tenderness and the author studied the cases shown in Table 68 Before the operation the degree of pain at both sites of the tonsils was recorded and the removed tonsils were examined pathologically for active inflammation especially of the difference of the size of lesion, which was compared with the pain recorded before the operation As demonstrated in Table 66 72 % of the cases were found to be true to the postulation. The author used the nasopharyngeal cotton applicator and measured the grade of tenderness as a diagnostic criterion for chronic tonsillitis. The applicator produced a sharp pain at the symmetric site of inflammation and the local treatment may relieve the pain or paraesthesia of the side of the neck.

4) Abnormal Feeling in the Median Pharyngolaryngeal Region (Laryngeal Neurosis)

We have a large number of patients who complain of abnormal feeling at the median portion of the throat They are afraid of cancer but most cases were found to have nasopharyngitis after the nasopharyngeal abrasion test Acute nasopharyngitis usually produces dryness

T ble 68 Tonsillitis and its tenderness.

P thological findings (preparation from the emoved materials)	
There is a difference between the right and the left	5 cases
There is slight difference between the right and the left	9 cases
right ≈ left	6 cases
Total	20 cases
Tenderness and pathological finding	
equal cases	13 cases (72.2)
unequal cases	4 cases
reverse case	1 case

and ill sensation at the dorsal part of the soft palate and often causes nasopharyngeal pain. Acute tonsillitis generally has a unilateral nasopharyngitis whereas the pain related to nasopharyngeal disorder occurs regardless of the laterality

5) Stiff Neck as a Result of Cervical Esophagitis

As discussed already diagnosis of nasopharyngitis was made easy by (1) examination of the smear preparation (2) observation of abrasion pain and (3) bleeding This method facilitates the determination of diseases that are invisible. Inflammation of the esophagus cannot be observed even with esophagoscopy but this method of diagnosing nasopharyngitis may be applicable in the confirmation of the site of lesion. For abrasion of the esophageal orifice the nasopharyngeal applicator is employed and the swab is inserted to the esophagus passing through the piriform sinus and the side walls and other parts are abrased Previously prepare the median and inferior nasopharyngeal abrasion preparation and examine them. The swabs obtained from the nasopharyngeal tract can be easily distinguished from those collected from the esopharyngeal abrasion. No report has been published on esophageal inflammation in the past but the swab applied to the site generally reveals intense erosion with abrasion pain and bleeding Stiff neck is one of the referred symptoms of esophagitis. Relation between stiff neck and esophagitis have a close resemblance to those between nasopharyngitis and headache especially in unilateral stiff neck. The local abrasion at the site of lesion produces sharp and heterotopic pain in the neck Severe bleeding was apparent because the swabs were filled with blood The smear preparation disclosed marked degeneration and exfoliation of epithelial cells Proliferation of infectious micro-organisms and appearance of leucocytes are quite similar to cases of nasopharyngitis (All cases obtained normal findings after continuous nasopharyngeal treatment with 1 $ZnCl_2$ solution) Stiff neck can be palliated in parallel to alleviation of esophageal lesion

Case No. 25

A 43 year old housewife with unilateral stiff neck.

History She had severe stiff neck a year ago

and needed daily massage. She was told that she had intense stiffness in the neck. (Stiffness is observed if caused by esophagitis and the improvement of the disease immediately relieves the patient of the stiff neck.) An internist and gynecologist diagnosed climacteric disturbances. Hormone treatment was prescribed but produced no effects. The patient had nasopharyngitis but was free from any other disorders. Unusual feeling of the esophagus was absent and no abnormalities were found in the cervical vertebrae.

Clinical findings Insertion of pharyngeal swabs to the esophagus produced sharp pain, especially the right wall which was symmetric to the site of stiff neck. The sharp pain produced by the swab abrasion passed through to the right side of the neck.

Post abrasion hemorrhage was observed and the symptom suggested cancer at the entrance of the esophagus. Epithelial cells in the smears were inspected microscopically and marked inflammation was detected by the presence of large number of neutrophic leucocytes, wandering cells, exfoliation of deformed epithelial cells and proliferation of bacteria. However no cancer cells were observed.

Clinical course The local treatment was carried out while preparing the tissue section for pathological examination.

The treatment was carried out with 1 $ZnCl_2$ solution every day. Rapid improvement was obtained and on the 5th day of treatment almost no bleeding was observed. On the 11th day abrasion pain was gone and the stiff neck was completely healed.

About 6 months later she caught cold and developed stiff neck in the left side. The esophageal abrasion caused marked bleeding. The usual treatment attained the disappearance of the stiffness in one week and no complaint has been heard from her since.

Localized esophagitis has been reported as a cause of esophageal neurosis but no reports have been published on stiff neck. Several reports on diagnosis of esophagitis did not describe precise clinical observations on esophageal changes, since no abrasion preparations were examined. Bosso investigated the relations between abrasion preparations and localized esophagitis.

Stiff neck is explained in relation to cervical syndrome. The cause of syndrome is ascribed to dislocation of cervical vertebrae, but the author considers esophageal inspection should be carried out first. Certain cases of clinically confirmed dislocation of cervical vertebra did not respond to stretch treatment but were successfully cured by the local abrasion treatment. Several cases with tangled relations were observed. A symmetric inflammation of the esophagus related to chronic tonsillitis, and the inflammation further influences the localized nasopharyngitis, which is derived from deformed nasal septum. (Reference is made to the Basic Study on symmetric relationships between inflammation and ORL disorders.)

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Case No. 26

H.S. A 20 year old girl with facial pain.

History About month before the patient felt pricking pain in the right cheek extending to the whole face. Also headache in the right forehead. Since then the pain was induced whenever she inhaled cool air became tired or while she was in an irritable condition, but did not occur while in warm room. (It was winter when she visited our clinic.) When the pain was severe nausea and vomiting attacked her. She occasionally complained of right otalgia. About 15 day before she had been admitted to the hospital and diagnosed as having trigeminal neuralgia, but no treatment alleviated the pain.

Clinical observations No abnormal changes were observed in the facial nerves. Blood and urine were normal. Pain was located at the right superior and inferior orbital foramen and at the root of the zygomatical arch. For 15 day internal medicine failed to produce any result and the patient was transferred to the ENT department.

No abnormality was obtained by routine ENT examinations.

Abrasion of the nasopharynx produced sharp pain which lasted for 3 hours with vomiting and nausea. However the pain at the right cheek and aural pain completely disappeared.

The treatment was continued to the next day but other medication was discontinued. The abrasion pain subsided and no bleeding was observed.

On the 5th day of treatment the abrasion pain

Also the author explained correlations between the smear preparation and the clinical pictures such as *abrasion pain and bleeding* and a physician may confirm the progress of inflammation from observation of the smears. Diagnostic criteria for chronic tonsillitis are based usually on gross examinations, such as unclear lacunae outlook, submerged tonsil and other changes that are visible to the eyes. The postoperative examinations often disclose intensive inflammation Clinically chronic tonsillitis is frequently associated with tenderness and the author studied the cases shown in Table 68 Before the operation the degree of pain at both sites of the tonsils was recorded and the removed tonsils were examined pathologically for active inflammation, especially of the difference of the size of lesion which was compared with the pain recorded before the operation. As demonstrated in Table 66 72 of the cases were found to be true to the postulation. The author used the nasopharyngeal cotton applicator and measured the grade of tenderness as a diagnostic criterion for chronic tonsillitis. The applicator produced a sharp pain at the symmetric site of inflammation and the local treatment may relieve the pain or paraesthesia of the side of the neck.

4) Abnormal Feeling in the Median Pharyngolaryngeal Region (Laryngeal Neurosis)

We have a large number of patients who complain of abnormal feeling at the median portion of the throat They are afraid of cancer but most cases were found to have nasopharyngitis after the nasopharyngeal abrasion test Acute nasopharyngitis usually produces dryness

Table 68 Tonsillitis and its tenderness.

Pathological findings (preparation from the removed materials)	
There is difference between the right and the left	5 cases
There is slight difference between the right and the left	9 cases
right = left	6 cases
Total	20 cases

Tenderness and pathological finding	
equal cases	13 cases (72.2)
unequal cases	4 cases
reverse case	1 case

and ill sensation at the dorsal part of the soft palate and often causes nasopharyngeal pain. *Acute tonsillitis* generally has a unilateral nasopharyngitis, whereas the pain related to nasopharyngeal disorder occurs regardless of the laterality

5) Stiff Neck as a Result of Cervical Esophagitis

As discussed already diagnosis of nasopharyngitis was made easy by (1) examination of the smear preparation (2) observation of abrasion pain and (3) bleeding This method facilitates the determination of diseases that are invisible. Inflammation of the esophagus cannot be observed even with esophagoscopy but this *method of diagnosing nasopharyngitis* may be applicable in the confirmation of the site of lesion For abrasion of the esophageal orifice the nasopharyngeal applicator is employed and the swab is inserted to the esophagus passing through the piriform sinus and the side walls and other parts are abrased Previously prepare the median and inferior nasopharyngeal abrasion preparation and examine them. The swabs obtained from the nasopharyngeal tract can be easily distinguished from those collected from the esopharyngeal abrasion No report has been published on esophageal inflammation in the past but the swab applied to the site generally reveals intense erosion with abrasion pain and bleeding Stiff neck is one of the referred symptoms of esophagitis. Relation between stiff neck and esophagitis have a close resemblance to those between nasopharyngitis and headache especially in unilateral stiff neck. The local abrasion at the site of lesion produces sharp and heterotopic pain in the neck. Severe bleeding was apparent because the swabs were filled with blood The smear preparation disclosed marked degeneration and exfoliation of epithelial cells Proliferation of infectious micro-organisms and appearance of leucocytes are quite similar to cases of nasopharyngitis (All cases obtained normal findings after continuous nasopharyngeal treatment with 1 $ZnCl_2$ solution.) Stiff neck can be palliated in parallel to alleviation of esophageal lesion

Case No. 25

A 43 year old housewife with unilateral stiff neck.

History She had severe stiff neck a year ago

5 Miscellaneous Facts Observed during the Course of Nasopharyngitis

Diabetes Mellitus

abetes is a disease considered to be incurable. nce it was found that diabetes was due to a fect of β-cells in Langerhans islands, t came possible to control this disease and abetic patients did not always become seri- sly ill. However the causes of diabetes are ll unknown and its fundamental treatment s not yet been found.

The nasopharyngeal treatment, however ems to make it possible to treat this incurable sease. The mechanism, by which diabetes sponds to the nasopharyngeal treatment, is ot known yet. However t is certain that iabetic patients ha nasopharyngitis, glu- osuria disappears and blood glucose becomes ormal by the local treatment of nasopharyn gitis—exactly the same method prescribed in his paper And as result t becomes possible o stop administration f insulin and other drugs in some cases. Examples are given elow

Case No. 28

S.K. A 46 year old male with dysacousis and diabetes.

Chief complaints Dysacousis, general for fatigue and urinary sugar

Diagnosis Diabetes and percepti dysacousis.

History of disease The patient had dysacousis in both sides since 7 to 8 years previously which was worsened by total exhaustion. I was found by hearing test that membranes of the tympanum on both sides were almost normal, but the patient had slight salpingitis, auditory acuity by air conduction was 40dB on both sides and there was decrease in bone conduc tion. The patient was diagnosed as ha ing percepti deafness. (Dysacousis of this patient was abated by nasopharyngeal and otosalpingian treatments. Some kinds of percepti deafness ere treated so efficiently by nasopharyngeal and otosalpingian treatments especially in babies, which will not be mentioned here.)

Since glucose was found in the urine 3 years previously the patient underwent internal treatment by a specialist in diabetes. Though he was administered sulfonylurea (1/2 tablet of Tolinase) glucosuria was always positive. He had neither thirst nor leanness.

H was rather obese.

A few microaneurysms were found by an oph- thalmoscopic examination. Blood glucose before the treatment was 136mg/dl.

Nasopharyngeal condition Nasal ca ities and pharynx were normal and no abnormalities were observed. When the nasopharynx was stimulated, significant abrasi pain and slight hemorrhage were observed. Abrasi pain lasted for about 2 hours.

Treatment and progress 1% $ZnCl_2$ solution (with small amount of Xylocain) was pplied to the nasopharyngeal wall every day

On the 1st day Severe pain when the solution was applied to the nasopharyngeal wall. Hemor rhage after $ZnCl_2$ application.

On the 2nd day Abrasi pain and hemor rhage. Glucosuria disappeared the day before.

On the 5th day As glucosuria became nega- tive, drug administration was stopped.

On the 6th day Glucosuria appeared again. No drug administration.

On the 20th day Glucosuria was positi both in the morning and in the evening. Blood glucose was 87mg/dl 2 hours after meal.

Almost no abrasi pain when $ZnCl_2$ solution was pplied to the nasopharynx.

On the 30th day Glucosuria was almost negati both in the morning and in the evening. Blood glucose was 78mg/dl.

On the 40th day Glucosuria was negati in morning and almost negati in the evening. Blood glucose was 120mg/dl.

On the 50th day; A few microaneurysms, which were observed previously disappeared completely by an ophthalmoscopic examination. Blood ssels were quite normal. Glucosuria was negati both in the morning and in the evening. Blood glucose was 80mg/dl.

On the 60th day Glucosuria was negati in the morning and in the evening. Blood glucose was 99mg/dl.

On the 70th day Glucosuria was negati in the morning and almost negati in the evening. Blood glucose was 84mg/dl. The nasopharyn- geal treatment was interrupted for about 15 days

disappeared No onset of pain was recorded since the commencement of the treatment Follow-up treatment was continued for two months and she never developed pain

This is a successful case of nasopharyngeal treatment which stopped facial pain and otalgia The case shoed that pain originating from nasopharyngeal inflammation caused and otalgia instead of headache. In the facial pain abrasion pain extends over to the anterior edge of nasopharyngeal base and in the otalgia abrasion pain often takes place in the ostium of the auditory tube The inflammation at the nasopharyngeal base often appears as pain of unknown origin on the alveolar process of the maxillary bone. For this reason several pieces of teeth were extracted and cancer was suspected The patient was relieved of pain by the treatment of nasopharyngeal abrasion Particularly nasopharyngeal treatment is useful in the treatment of toothache. The author described how pain or uneasiness of unknown cause originated from the various inflammation sources. At the close of this chapter I would like to refer to certain cases involving blood pressure changes and neurosis.

Case No 27

A 51 year old female with complaints of left side migrain paraesthesia of the neck on the left side. Stiff neck on the left side. Pain in both knees. Systemic tiredness. Hypotension and irritability

History She was constitutionally weak and susceptible to colds. 10 years ago she developed symptoms and was diagnosed as having menopausal disorders and was given hormone preparations. No effect was attained. Menopause ended before 5 years but the symptoms were exacerbated Visited an orthopedic surgeon and was diagnosed as having a cervical syndrome. Traction therapy was tried for 6 months but no effect was attained. Recently the symptoms were aggravated and tinnitus developed. She visited the clinic.

Clinical observation Nasopharyngeal abrasion test exhibited intense bleeding and severe post abrasive pain which was heavier on the left side. High degree of deformity was observed in the left meatus nasi septum and the reason for severe symptoms on the left side was found. The tonsil had tenderness and postabrasive pain Esophageal application of a swab produced severe pain at the left side of the nasopharynx. A marked inflammation was observed in the left meatus nasi septum.

Clinical course Nasopharyngeal esophageal abrasion with the cotton applicator dipped into 1 $ZnCl_2$ reduced stiff neck and migrain on the 5th day of the treatment. After one month of continuous treatment the pain in both knees subsided and normal blood pressure was obtained. Generalized fatigue was gone and she could sleep well The patient continued treatment for 6 months and found that she had menstruation with the aid of hormone administration.

The psychological symptoms such as internal or psychiatric irritation are often complained of by the patients. They are so-called masked depression and the physician should remember the above case

5 Miscellaneous Facts Observed during the *Course* of Nasopharyngitis

1) Diabetes Mellitus

Diabetes is a disease considered to be incurable. Since it was found that diabetes was due to a defect of β-cells in Langerhans' islands, it became possible to control this disease and diabetic patients did not always become seriously ill. However the causes of diabetes are still unknown and its fundamental treatment has not yet been found.

The nasopharyngeal treatment, however seems to make it possible to treat this incurable disease. The mechanism, by which diabetes responds to the nasopharyngeal treatment, is not known yet. However it is certain that diabetic patients have nasopharyngitis, glucosuria disappears and blood glucose becomes normal by the local treatment of nasopharyngitis—exactly the same method prescribed in this paper. And as a result it becomes possible to stop administration of insulin and other drugs in some cases. Examples are given below.

Case No. 28

S.K. A 46 year old male with dysacousis and diabetes.

Chief complaints: Dysacousis, general fatigue and urinary sugar.

Diagnosis: Diabetes and perceptive dysacousis.

History of disease: The patient had dysacousis in both sides since 7 to 8 years previously which was worsened by total exhaustion. It was found by hearing test that membranes of the tympanum on both sides were almost normal, but the patient had slight salpingitis, auditory acuity by air conduction was 40dB on both sides and there was decrease in bone conduction. The patient was diagnosed as having perceptive deafness. (Dysacousis of this patient was abated by nasopharyngeal and otosalpingian treatments. Some kinds of perceptive deafness were treated so efficiently by nasopharyngeal and otosalpingian treatments especially in babies, which will not be mentioned here.)

Since glucose was found in the urine 3 years previously the patient underwent internal treatment by specialist in diabetes. Though he was administered sulfonylurea (1/2 tablet of Tolinase) glucosuria was always positive. He had neither thirst nor leanness.

He was rather obese.

A few microaneurysma were found by an ophthalmoscopic examination. Blood glucose before the treatment was 156mg/dl.

Nasopharyngeal condition: Nasal cavities and pharynx were normal and no abnormalities were observed. When the nasopharynx was stimulated, significant abrasive pain and slight hemorrhage were observed. Abrasive pain lasted for about 2 hours.

Treatment and progress: 1% $ZnCl_2$ solution (with small amount of Xylocain) was applied to the nasopharyngeal wall every day.

On the 1st day: Severe pain when the solution was applied to the nasopharyngeal wall. Hemorrhage after $ZnCl_2$ application.

On the 2nd day: Abrasive pain and hemorrhage. Glucosuria disappeared the day before.

On the 5th day: As glucosuria became negative, drug administration was stopped.

On the 6th day: Glucosuria appeared again. No drug administration.

On the 20th day: Glucosuria was positive both in the morning and in the evening. Blood glucose was 87mg/dl 2 hours after meal.

Almost no abrasive pain when $ZnCl_2$ solution was applied to the nasopharynx.

On the 30th day: Glucosuria was almost negative both in the morning and in the evening. Blood glucose was 78mg/dl.

On the 40th day: Glucosuria was negative in morning and almost negative in the evening. Blood glucose was 120mg/dl.

On the 50th day: A few microaneurysma, which were observed previously disappeared completely by an ophthalmoscopic examination. Blood vessels were quite normal. Glucosuria was negative both in the morning and in the evening. Blood glucose was 80mg/dl.

On the 60th day: Glucosuria was negative in the morning and in the evening. Blood glucose was 99mg/dl.

On the 70th day: *Glucosuria* was negative in the morning and almost negative in the evening. Blood glucose was 84mg/dl. The nasopharyngeal treatment was interrupted for about 15 days

because of a trip. The patient caught cold during this interruption.

On the 90th day Severe abrasive pain when $ZnCl_2$ solution was applied in nasopharynx. Slight bleeding Glucosuria was positive in the morning and almost negative in the evening Blood glucose was 112mg/dl.

On the 110th day Glucosuria was negative in the morning and almost negative in the evening Blood glucose was 83mg/dl.

The patient is still under treatment

Case No 29 (Fig 75)

K.K. A 73 year old male with diabetes.

Chief complaints General fatigue furuncle of the head and visual disorders.

Diagnosis Diabetes, diabetic retinopathy (Scott II) aphthous stomatitis (habitual) alveolar pyorrhea and hypertension.

History of diseases The patient had total exhaustion since 10 years before and furuncles were easily formed on the head. Around that time glucosuria was found, which could not be controlled thoroughly in spite of insulin administration and glucosuria never disappeared.

Tests When a glucose tolerance test (50 g glucose) was conducted before starting the nasopharyngeal treatment blood glucose followed the dotted line in Fig 75 and glucosuria was also positive. Blood pressure was 208–94 Bleeding in the retina was observed by an ophthalmoscopic examination and several arteriolo-aneurysms were observed. Marked abrasive pain and bleeding after stimulation of the nasopharynx were observed. Transformation and desquamation of the epithelial cells and appearance of neutrophiles were observed in the smears. Staphylococcus aureus was found.

Treatment A small amount of Xylocain was added to 1 $ZnCl_2$ solution and applied throughly to the nasopharynx. When this treatment was continued every day for one month, glucosuria disappeared, both fasting blood glucose and a glucose tolerance test were significantly improved (the solid line in Fig 75) Blood pressure decreased to 158–80 (refer to the paragraph of blood pressure) and aphtha disappeared also (refer to the paragraph of aphtha) Bleeding in the retina could not be seen thereafter

In the observation for the next 2 years, glucosuria was found two times when the patient caught cold, however it disappeared about one week be the nasopharyngeal treatment. Drugs for diabetes, such as insulin, are not administered now

About 30 patients with diabetes were treated only by the local nasopharyngeal treatment by now In most of them blood glucose returned to the normal value or came close to it glucosuria disappeared and various symptoms, which accompanied diabetes, also disappeared. Fig 76 showed glucose tolerance tests of 9 patients, to whom 50g of glucose were administered before and after the nasopharyngeal treatment. Except for one patient (I K. 35 year-old male) blood glucose became normal after the treatment (solid lines) and glucosuria disappeared Even in the patient who took a serious turn progress thereafter was favorable and glucosuria was reported to have disappeared As shown in Fig 77 (2) fasting blood glucose decreased after 2 months.

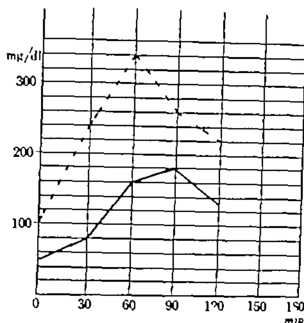


Fig. 75. Case No. 29 (K.K. 73 Y ♂) Glucose (50 g) tolerance test.

Fig 77 showed changes of fasting blood glucose by the nasopharyngeal treatment As blood glucose during hunger was reported as 60 100 mg dl these values shown in Fig 76 could not be called normal Judging from the disappearance of glucosuria however it could not be denied that the nasopharyngeal treatment was fairly effective It was interesting to know that by the nasopharyngeal treatment glucosuria disappeared and thirst polyphagia emaciation and exhaustion disappeared in most patients.

Besides changes in the pancreas, changes in the blood vessels a

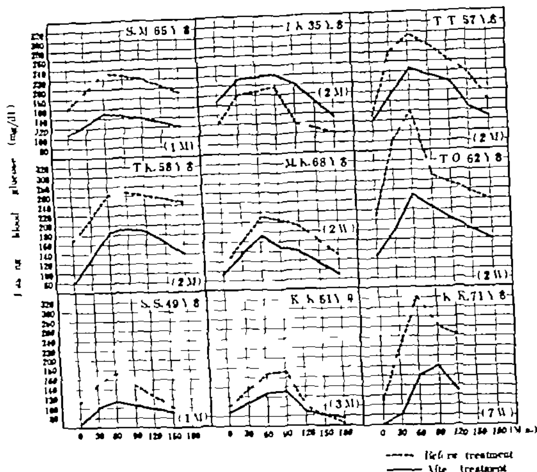


Fig. 76. Diabetes and nasopharyngeal treatment.

condition of diabetes. The changes in the blood vessels are the so-called Kimmelstiel-Wilson's symptom and are the changes in small blood vessels such as those of the kidneys, which the author has never studied. In the eyeground vessels, small aneurysms are often found, which cause bleeding of the eyeground when ruptured. These changes in the blood vessels caused by diabetes are said to be difficult to cure and bleeding of the eyeground might result in blindness after several relapses. It was interesting however that in both 2 patients with bleeding of the eyeground, no bleeding was observed after starting the nasopharyngeal treatment and also in another case with aneurysma, it was found to have completely disappeared after 2 months.

Though the nasopharyngeal treatment was conducted on the patients with Brittle type diabetes, normalization of blood and urinary glucose was not necessarily easy and complete recovery could not be expected. Even in such cases, however, it was possible to improve the symptoms remarkably with the nasopharyngeal treatment. Therefore they might have recovered completely if the treatment was continued for a longer term. A patient was found to have Brittle type diabetes after falling into a comatose state. In spite of various treatments with insulin, the patient lost body weight, had thirst and hypoglycemic fits repeatedly. By starting the nasopharyngeal treatment, however, his diabetic state was controlled and the amount of insulin could be reduced significantly compared to that used before the nasopharyngeal treatment though

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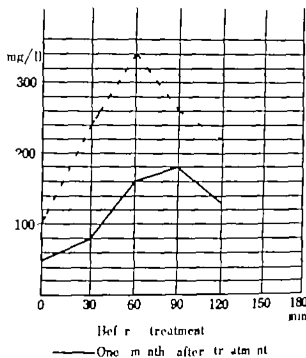


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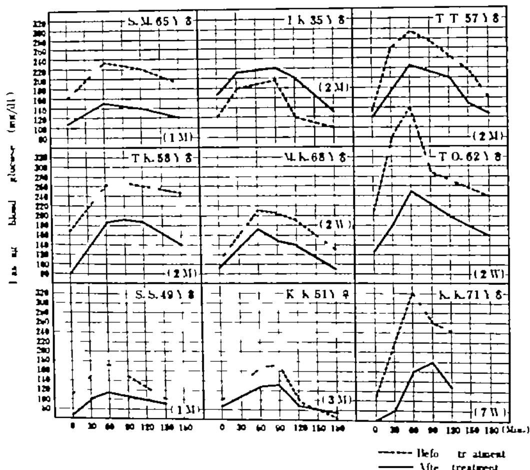


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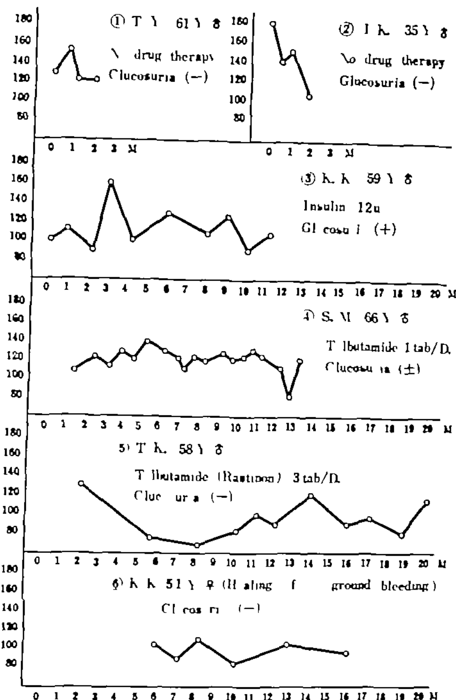


Fig. 77 Course of fasting blood glucose.

insulin administration itself could not be stopped The patient was working so busily after leaving the hospital that neither the treatment nor the tests could be continued When asked on the phone 2 years after his leaving the hospital he said that he was working well It was interesting that the patient always had abnormal feeling in the nasopharynx before he became conscious of symptoms of aggravation of diabetes and he complained of it to a doctor but the doctor never took it seriously This is a case in which a patient became conscious of the relation between diabetes and nasopharyngitis.

The idea to improve or cure diabetes by the nasopharyngeal treatment is not based on theoretical inference It is rather based on the experience that diabetes combines with rheumatism and hypertension, and when the nasopharyngeal treatment is conducted for these diseases, diabetes is also improved.

The causes of diabetes are not yet known.

Pregnancy heredity and inflammation are given as proximate causes, but none of them are certain. For example, the relation between inflammation and diabetes is such that diabetes is worsened or started with an attack of acute inflammation.

Most of the patients with diabetes has significant nasopharyngitis. Nasopharyngitis progresses by repeating acute inflammation. Therefore it is possible to look for causes of diabetes in the category of autoimmune diseases resulting from nasopharyngitis. For the autoimmune diseases, however discovery of an autoantibody is necessary as a matter of course.

There is a thought that diabetes may be an autoimmune disease. Though autoantibody for diabetes has not yet been found, the above supposition is based on the following facts. Namely (1) diabetes is often combined with pernicious anemia, which is an autoimmune disease (2) thyroid antibody is often found in patients with juvenile diabetes (2 patients with Hashimoto's Disease, one of the autoimmune diseases of the thyroid) were cured by the nasopharyngeal treatment, (3) fluorescent γ-globulin and infiltration of lymphocytes are often observed in pancreatic specimens of patients with diabetes. Anyway it is certain that diabetes is improved remarkably by the nasopharyngeal treatment. It is not clear yet whether the mechanism of its crisis is due to an autoimmune disease or continuous extrinsic stimulation of the hypothalamus, such as CRF on adrenal and TRF on thyroid, causes dysfunction of Langerhans islands.

2) Thyroids

Nephritis is said to be a focal infectious disease of parenchymatous organs or an autoimmune disease. Nephritis often responds to nasopharyngeal treatment like rheumatism. Some kinds of thyroids are also thought to be diseases of autoimmunization and autoantibodies or fluorescent substances are demonstrated. The following are cases which were diagnosed as having the so-called Hashimoto Disease and were cured relatively fast by nasopharyngeal treatment. (As the author had only cases, it is doubtful whether these cases healed by the nasopharyngeal treatment had any universal validity. However the fact could not be denied.)

Case No. 30

K.S., 55 year old male with hypothyreosis.

Chief complaints: Edema of the neck.

History: Since few months before, the patient started to feel the collar of his shirt very tight and he visited the hospital with suspicion of *laryngeal* tumor. Edema was found mainly in the anterior jugulum and was also found in the face, nape, *the back of the hand, and the instep of the foot.* One eyelid was swollen. He was unable to speak distinctly. Nephritis could be denied as urinary test was normal. The skin was dull and dry. His complexion was yellowish and did not look well. (No abnormalities were found in liver function and bile excretion.) Swelling of the skin was not so bad as to make hollows. The patient had lost his appetite recently. His movements became slow and he acted passively *in everything.* Blood pressure was 93–80.

Condition: The laryngeal mucosa was slightly flared. Otorhinological condition was missing. Edema of the anterior jugulum was suggestive of myxedema of the thyroid.

Urinary condition was normal (Protein (—) glucose (—)) cardiac hypertrophy was found by X-ray photo *and slight block was found in ECG* (ST was high). No abnormalities were observed in other organs.

B.M.R. (Basal metabolic rate): —22%

Thyroid hormone test 20.4*

Adrenal hormone test 17KS 3.4 mg/day

17 OHCS 22*

From the scintigram it was found that the picture of the thyroid was faint and scattered, and incorporation was diffusely impaired throughout the organ.

Diagnosis: Chronic thyroiditis.

Treatment: 30 mg of thyroid powder was administered at internal medicine, but the patient decided to undergo the nasopharyngeal treatment instead of taking the drug. At the beginning he complained of severe pain caused by the local nasopharyngeal *treatment and bleeding* was observed after application of 1% $ZnCl_2$ solution. In spite of that he felt better after the treatment, and thereafter the nasopharyngeal treatment was continued daily for one month.

(1) Basal metabolic rate after 1 month was 1%.
(2) Cardiac hypertrophy was improved significantly *and became normal in X-ray* photos.
(3) However no change was observed in ECG and the block was still observed.
(4) Blood pressure was 110/80.
(5) Swelling of the neck disappeared.

Though the patient stopped visiting the hospital for certain reasons, he was fine after 6 months. An important point in this case was that BMR,

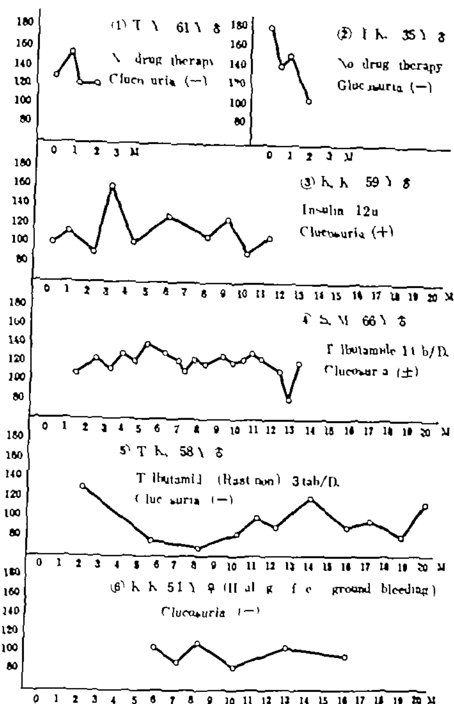


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K.S., 55 year old male with hypothyroidism.

Chief complaint Edema of the neck.

History Since a few months before, the patient started to feel the collar of his shirt very tight and he visited the hospital with suspicion of laryngeal tumor. Edema was found mainly in the anterior jugulum and was also found in the face, nape, the back of the hand, and the instep of the foot. One eyelid was swollen. He was unable to speak distinctly. Nephritis could be denied as urinary test was normal. The skin was dull and dry. His complexion was yellowish and did not look well. (No abnormalities were found in liver function and bile excretion.) Swelling of the skin was not so bad as to make hollows. The patient had lost his appetite recently. His movements became slow and he acted passively in everything. Blood pressure was 94-80.

Condition The laryngeal mucosa was slightly flared. Otorhinological condition was missing. Edema of the anterior jugulum was suggestive of myxedema of the thyroid.

Urinary condition was normal (Protein (−) glucose (−)) cardiac hypertrophy was found by X-ray photo and slight block was found in ECG (ST was high). No abnormalities were observed in other organs.

B.M.R. (Basal metabolic rate) −22%
Thyroid hormone test 20.4%
Adrenal hormone test: 17KS 3.4 mg/day
17 OHCS 22%

From the scintigram it was found that the picture of the thyroid was faint and scattered, and incorporation was diffusely impaired throughout the organ.

Diagnosis Chronic thyroiditis.

Treatment 30 mg of thyroid powder was administered at internal medicine, but the patient decided to undergo the nasopharyngeal treatment instead of taking the drug. At the beginning he complained of sever pain caused by the local nasopharyngeal treatment and bleeding was observed after application of 1% $ZnCl_2$ solution. *In spite of that he felt better after the treatment, and thereafter the nasopharyngeal treatment was continued daily for one month.*

(1) Basal metabolic rate after 1 month was 1%.
(2) Cardiac hypertrophy was improved significantly and became normal in X-ray photos.
(3) However no change was observed in ECG and the block was still observed.
(4) Blood pressure was 110/80.
(5) Swelling of the neck disappeared.

Though the patient stopped visiting the hospital for certain reasons, he was fine after 6 months. An important point in this case was that BMR,

which was −11 at the beginning, was improved to +1 after 1 month of the nasopharyngeal treatment. This was a case of the so-called Hashimoto's Disease, dysfunction of the thyroid, which was thought to be an autoimmune disease of the thyroid. Though it is said that there is no special treatment for this disease other than administration of hormones, it was improved significantly by the nasopharyngeal treatment. The author found another such case.

The author conducted the nasopharyngeal treatment on 5 patients with hyperfunction of the thyroid and succeeded in normalizing the basal metabolic rate, increasing the body weight and eliminating of the thyroid symptoms. Swelling of the thyroid however did not disappear in these cases.

3) Slight Fever

Tonsillopathy is often given as a cause of pyrexia of unknown origins. When pyrexia lasts in spite of tonsillectomy nasopharyngitis is often found as a cause for that. When smears of nasopharynx of these patients are tested directly without being too particular about tonsillitis (regardless of the presence of tonsillitis) severe inflammation is observed (bleeding after abrasion and the presence of erosion are found) and pyrexia of unknown origins is controlled in many cases by the local nasopharyngeal treatment. This is often observed in the case when pyrexia lasts after catching cold (It can be *thought as acute nasopharyngitis.*)

Case No. 31

E.N 11 year old girl with slight fever

History of diseases 3 months before visiting the hospital the patient complained of headache and left school earlier than usual. Her body temperature was 37.3 C and she was administered an antibiotic by a specialist in pediatrics. Fever however was not alleviated. Then the patient was sent to an otorhinologist, who told that she was in good condition after examining her throat. (This is an important point!) The body temperature still stayed around 37.5 C after the laryngeal examination. About 2 months before visiting our hospital the patient was sent to the internal medicin dept. of university hospital when sh was told sh was normal after a tot l examinat on, such as urinary tests, blood tests X ray photos, etc The patient was still feverish, complained of headache and exhaust on lost her will to tudy and missed school

Otorhinological condition No changes were observed in general otorhinological tests. Both palate and tonsils were normal. However th patient complained of severe pain after abrasion of the nasopharynx with a cotton swab and a large quantity of blood came out after the abrasion. Inflammation was observed clearly in the smeared specimens, which suggested the presence of erosion in the nasopharynx. (In children younger than this age the conditions mentioned above were often observed after abrasion of nasopharynx.)

Clinical course Treatments other than application of 1 $ZnCl_2$ solution (with a small amount of Xylocain added) every day to the nasopharynx were rejected. Antifebriles were also prohibited to see the effect of the nasopharyngeal treatment on febricula. After starting the nasopharyngeal treatment, the patient progressed favorably a normal temperature was obtained 3 days after starting the treatment and the temperature never went up. On the 20th day however the patient caught cold, the body temperature went up to 37.3 °C, and abrasive pain and bleeding after abrasion of the nasopharynx came back again (The author thinks that a cold is a symptom of the autonomic nervous system, which comes out after acute nasopharyngitis. In fact some patients complained of catching cold immediately after application of a medical solution to the nasopharynx.) This condition disappeared by conducting the nasopharyngeal treatment for a few days, and the body temperature returned to its normal value. As the body temperature stayed normal, the treatment was stopped after 3 months. The patient was observed for 1 year after that and she never had an attack of fever during this period.

Slight fever is encountered in children very often. According to a survey those whose axillary temperature exceeded 37 1 C were 26, 47 2 and 62 in the morning for test periods of 5 10 and 15 minutes respectively and 41 0 64 4 and 80.2 in the afternoon. Though it was concluded that febricula was their normal physiological condition, it would be difficult to conclud that so many school children (about 0% of them) had nasopharyngitis, an abnormal condition. When the nasopharyngeal treatment was conducted on some children, who were chosen arbitrarily from such school children with febricula, their body temperature returned to normal and they became extremely energetic.

Habitual pyrexia of school ch ldren or essential pyrexia) is not so simple as that mentioned abov It is related to diseases, such as rheumatic fever (h gh ASL-O alu) subsepsis allergica, habitual cold, bronchial asthma, habitual purpura and hemopathy characterized nd treated according to each disease On the contrary th uthor thinks that the diseases, which should belong to the same category appeared w th arious faces.

The reason for this is that all of these diseases are combined with nasopharyngitis, and they are often cured by the local treatment of the nasopharynx.

4) Epistaxis

The nasopharyngeal treatment is very effective on epistaxis in some cases. As local hemostasia was thought to be most important in the past, a tampon and cauterization were used. Ligation of A. sphenopalatina and Aa. ethmoidales was also conducted locally.

The author however obtained successful results by application of 1% $ZnCl_2$ solution to the nasopharynx of the patients with epistaxis. The idea was obtained from finding that in habitual epistaxis of children (for example, rhinorrhagia caused by the adenoids) severe inflammation was often observed in the nasopharynx and by treating the inflammation locally (application of 1% $ZnCl_2$ solution to the nasopharynx) the habitual epistaxis was cured.

The reason is probably that inflammation in the nasopharynx, which extended to Locus Kiesselbachi and other nasal mucous membrane through rhinal ground and nasal mucous membrane, became susceptible to bleeding. Fortunately the nasopharyngeal treatment was extremely effective on epistaxis and hemostasia was obtained by only one treatment as shown in the example below. Though it is doubtful that nasopharyngitis is a cause of the inflammation when such quick hemostasia is obtained, nasopharyngitis and nasal vestibulitis could be causes of habitual epistaxis of school children.

There is no need to think that inflammation of nasal vestibule is extended from the nasopharynx. In the transitional zone of Apertula piriformis to the mucous membrane there was inflammation severer than that found in the nasopharynx in many cases. This is probably because bigger molecules of dust in the air which come and go by respiration, adhere to the mucous membrane around the nasal vestibule and nostrils and cause inflammation there. Judging from this it should be said that L. Kiesselbachii is simply apt to cause inflammation and bleeding rather than that L. Kiesselbachii is apt to bleed because of its being rich in blood vessels.

Case No. 2.

8 year old boy with habitual epistaxis.

History of disease Since he was 6 years old, he was susceptible to epistaxis. In the beginning bleeding could be stopped relatively easily by plugging the nasal cavity with cotton and cooling the bridge of the nose at home. Epistaxis became severer and severer and the patient visited an otorhinologist. There was no abnormal component in the blood, no prolongation of bleeding time and no special causes of bleeding such as tumor. However the patient was found to have rhinitis anterior sicca. The bleeding was said to be from L. Kiesselbachii (Little's area) which was cauterized, and a styptic was administered.

Condition There was inflammation in the nasal vestibule. Especially the mucous membrane of L. Kiesselbachii was cyanotic, blood vessels were cut here and there and some bleeding was observed.

Treatment A tampon was rejected and 1% $ZnCl_2$ solution was applied to the nasopharynx. The patient complained of severe pain and large amount of bleeding was observed from nasopharynx. (There was no need to worry about the bleeding as it was thought to be superficial.) The patient was diagnosed as having severe nasopharyngitis by testing smears.

From the day of starting the nasopharyngeal treatment, epistaxis stopped. After 1 month of daily nasopharyngeal treatment, the treatment was stopped. The patient was observed for 2 years after that without any bleeding.

When the nasopharynx of patients with habitual epistaxis of unknown origins was tested, severe inflammation (erosion) was found and bleeding was observed on application of $ZnCl_2$ solution in many cases. The bleeding was stopped by the nasopharyngeal treatment. It was demonstrated that fibrinolysis was accelerated by the nasopharyngeal stimulation and the acceleration was significant when the patient had acute nasopharyngitis. It was also observed that the accelerated fibrinolysis was restored to its normal state by the nasopharyngeal treatment. Though this might not be all that activated the mechanism of hemostasis by the nasopharyngeal treatment, this possibly played a part. The following is a case of more serious adult epistaxis.

Case No. 33

A.T. 18 year old male with epistaxis (thrombocytopathia).

History of disease Since he was 3 years old, the patient had nose bleeding about 2 times a year. His younger brother had the same trouble.

When he got hurt, it was difficult to stop the bleeding Frequency and quantity of bleeding increased gradually When he was in the 3rd grade of elementary school (9 years old) the patient was hospitalized because of severe nose bleed and was given a transfusion of 100ml of blood every day Though the epistaxis stopped in one day he stayed at the hospital for 3 to 4 months because of anemia. When he was in the 5th grade of elementary school (11 years old) patient was hospitalized again for epistaxis.
After that he went to the hospital 1 to 2 times a year because of epistaxis. Since he was in the 1st grade of junior high school (13 years old) the patient experienced bleeding from the gingiva occasionally which stopped spontaneously
On July 20th of 1970 he had anorexia and pain at hypochondrium and was diagnosed to have duodenal ulcer His chief complaints were nasal bleeding and hypochondrial pain and he was taken to internal medicine.
Condition Blood pressure was 1?6–80 Bleeding time was more than 20 minutes. Coagula tion time was 5 minutes. Rumpel Leede was (⧻) Blood platelets were basophilic and large. Hb 13 1 RBC 440×10⁴ Ht 42 Ret 4 Pl 1 3 WBC 5 600
CRP (−) ASLO 50 WR (−) LE cell (−) Thoracic XP normal.
Bleeding from the nose increased 5 days after hospitalization, and Ht, which was 42 when he was hosp talized decreased to 25 Hemostasis could not be obtained in spite of administering various drugs. An otorhinologist on duty was asked to visit the patient and bleeding was found to occur from the free end of the inferior turbinate body and L. Kiesselbachii. An intranasal tampon was used but blood was oozing from the tampon The tampon was changed every day and th bleeding area was cauterized The cauterization however caused bleeding from another place When use of a tampon was stopped bleeding started again and thereafter it could not be stopped
Twenty days after starting the otorhinological treatment 1 $ZnCl_2$ solution was applied to the nasopharynx for trial Though severe pain and bleeding from the nasopharynx were observed after the application of 1 $ZnCl_2$ solution nose bleed stopped on that day A tampon was removed the day after w thout any hemorrhage The nasopharyngeal treatment was continued for about 1 m nth and the patient left the hosp tal after making sure that no mor bleeding occurred.
As the patient never visited our hospital thereafter his present cond tion is not known. It is certain however that the nasopharyngeal treatment was effecti e in this case.

5) Various Cases Cured by Vasodilatation

It was mentioned in the basic chapter that nasopharyngitis stimulated the peripheral vasomotor nerve. It was not clear however by what kind of mechanism it occurred clinically In the example shown in the preceeding para graph it was simply a clinical experience that the nasopharyngeal irritation and the treatment of nasopharyngitis were extremely effective on hemostasis of epistaxis and the reason could not be explained.

It could be thought however that the nasopharyngeal treatment affected the opening and closing of the vascular lumen. Therefore the author tried the nasopharyngeal treatment on a few diseases, which were caused by dysfunction of the vasomotor nerve. Though there were only a few cases the author thought that this was a hopeful experiment and wanted to study more of these cases.

The 1st case was a 58 year old woman with thromboarteritis obliterans. Her right leg below the talocrural articulation was all black because of necrosis. The right femoral artery could hardly be palpated the right pelvic limb was discolored as far as the upper femur and the patient was inoperable. When the nasopharyngeal treatment was started, circulation of the blood was rapidly recovered and amputation of the foot became possible after 1 week of the nasopharyngeal treatment.

The 2nd case was a 63 year old male with a fit of acute cerebral embolism. The patient was hospi talized the day after the fit. He had total paralysis f the right arm and foot and right facial nerve. The nasopharyngeal treatment was started i mmediately after hospitalization. From the day of starting the treatment, the patient showed signs of recovery After 10 days he could t up in bed by himself and after 2 weeks he could walk with the help of cane. In th 4th week he did not need the cane anymore and in the 2nd month grasping power of both hands became equal.

This patient might have recovered spontaneously but, this was a case of complet recovery of total hem plegia in 2 months using the nasophary geal treatment. Those cases, which a e called cerebral thrombosis or embolism, are of not thrombotic but spastic nature according to my opinion. When the angiospasm lasts for a long period there arises thrombus or neurysm

The 3rd case was a 32 year old woman with possible Raynaud Disease When she was exposed to cold ai her hands became pale or cyanotic. The patient visited various doctors for 10 years but was told that her disease was incurable. Thougl the ymptoms were improved rapidly after tart ng the nasophary n-

geal treatment, it was not cured completely. It was interesting to observe that her hands and fingers, which were cyanotic, became rosy immediately after application of % $ZnCl_2$ solution in nasopharynx.

6) Cases which were Thought to Have Dysfunction of the Central Nervous System

The patient mentioned in the paragraph about dysfunction of the autonomic nervous system was nervous and was not satisfied with her daily life. However she became cheerful after the nasopharyngeal treatment. A similar change was often observed in cases of O D. As mentioned in the paragraph about the autonomic nervous system, depression was thought to arise for a reason similar to that of masked depression. In the patient with masked depression, depression appears when he has incurable rheumatism or hypertension. Nasopharyngitis could be a cause of rheumatism or hypertension as mentioned before, and therefore nasopharyngitis might be a cause of such depression. If so there might be kind of depression induced by nasopharyngitis among the depressions which are not combined with rheumatism or hypertension. As the nasopharyngeal stimulation caused contraction of the peripheral blood vessels, it also might affect cerebral blood vessels. When changes in the arteries of the eyeground were tested by the nasopharyngeal stimulation, changes similar to those in digital blood vessels were observed. It could not be said decidedly as the author had only a few cases. Many patients felt sleepy immediately after the nasopharyngeal treatment and became clearheaded after while, which might be proof that nasopharyngitis affected cerebral blood flow. The following is a case of depression in which nasopharyngeal treatment was conducted.

Case No. 4

K. O. 16-year-old boy with depression

The patient had severe headache since 4 years before and was diagnosed as having vascular headache at the cerebral surgery department. Though he was treated for 1 year, the headache was not improved. He became enervated and slow in reaction. He was examined again at the cerebral surgery department and said to be not pathologic. He was sent to the psychiatric department and diagnosed as having depression. After he was hospitalized and administered various drugs, he suffered from gastrointestinal disorders and anorexia, which became worse and worse, and got a mask-like face. Though he used to be cheerful and laugh a lot, recently he did not laugh at all.

He was said to have nasal allergy in his childhood. He had a stuffy nose since that time. A member of his family thought that the present symptoms might be caused by the nasal allergy in his childhood, and took him to our hospital. He had a mask-like face without any emotional expression, did not answer our questions and did not laugh at all.

The inferior turbinate was enlarged, which showed the presence of severe hypertrophic rhinitis. Nasopharyngeal treatment (refer to the paragraph on nasal allergy) was decided on. When the nasopharynx was abraded, severe pain and bleeding of a large quantity were observed. As severe inflammation was observed also in the smeared specimens, it was diagnosed as nasopharyngitis and the treatment was started.

Treatment: 1% $ZnCl_2$ solution was applied to the nasopharyngeal mucous membrane every day. Drugs prescribed at the psychiatric department were rejected. Though significant abnormal pain and hemorrhage were observed at the beginning, bleeding decreased markedly after 5 days. After 2 weeks, abnormal pain was reduced and no more bleeding was observed. Headache was also improved remarkably. One month after starting the treatment, headache disappeared, the stuffy nose was also improved and hypertrophy of the inferior turbinate body disappeared also. Since then the patient started to talk little by little and laugh from time to time. His family was so happy about his progress. He left the psychiatric department and became an out-patient. He became cheerful after 2 months and spoke cheerfully about his attending school from the next semester.

It is not known whether this was genuine depression or not. According to a psychiatrist, there are such cases among genuine depression cases, and classification can be made only by watching their progress. If so, it seemed but worth studying whether those whose condition at the beginning was the same, but whose progress was unfavorable, became genuinely depressive.

7) Nocturnal Enuresis

It was discovered accidentally that the nasopharyngeal treatment was effective on nocturnal enuresis, and there was no theoretical relation between them. The first case was a boy with infantile asthma, on whom the nasopharyngeal treatment was conducted and nocturnal enuresis disappeared 3 days after starting the treatment. After that 6 cases with enuresis

When he got hurt, it was difficult to stop the bleeding Frequency and quantity of bleeding increased gradually When he was in the 3rd grade of elementary school (9 years old) the patient was hospitalized because of severe nose bleed and was given a transfusion of 100ml of blood every day Though the epistaxis stopped in one day he stayed at the hospital for 3 to 4 months because of anemia. When he was in the 5th grade of elementary school (11 years old) patient was hospitalized again for epistaxis.
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Table 69 Subjective symptoms of influenza prevailing in 1950–1957

Year Type / Symptoms	1950 winter Type B	1951 winter Type A	1953 winter Type A	957 summer Type A_g	1957 fall Type B_g
Headache	69%	75*	67	87*	82*
Cough	76	62	65		64
Sputum	27	28	35	44	50
Myalgia and Arthralgia	16	29	20	43	26
Sore throat	33	36	37	51	48
Nasal occlusion Nasal discharge	50	67	59	37	56
Anorexia	32	50	41	86	62
Fatigue	30	43	45	43	32
Epistaxis	6	4	15	12	12
Sweating	—	—	—	60	.6

by Kitamoto et al. is thought to be this kind of pain, namely nasopharyngeal pain. Genuine oropharyngeal pain appears mostly as unilateral tonsillar pain, and rarely appears in the median portion.

(3) Headache in case of a common cold can be explained as the pain radiated from the nasopharyngeal wall or the wall of the inferior nasal meatus as shown in the paragraph on headache and nasopharyngitis.

(4) There is a close relationship between nasopharyngitis and pyrexia as mentioned previously in the paragraph on pyrexia.

( ) It was reported previously that so-called nasal allergy was closely related to nasopharyngitis. Nasal symptoms combined with acute nasopharyngitis are thought to be kind of irritation symptoms. The so-called catarrhal rhinitis was demonstrated to be closely related to nasopharyngitis.

(6) Open nasal voice which appears in the first stage of common cold together with an abnormal feeling in the nasopharynx or pharynx. Nasal sounds such as m, n and ŋ twang characteristic ... is thought to be Rhinolalia aperta due to slight paresis of the soft palate.

7 When the nasopharynx of the patients with chronic abnormal feeling of the body was abraded with cotton swab moistered with 1 $ZnCl_2$ solution they complained of severe fatigue immediately after the treatment. In the treatment of nasopharyngitis or in the nasopharyngeal stimulation, the patients were tacked by unusual exhaustion and could not even stand up. This was probably related to exhaustion caused by the common cold.

(8) Some patients complained of catching cold immediately after the nasopharyngeal treatment (application of a drug solution). It was thought that reaction to local stimulation of the nasopharynx appeared locally and totally which was an interesting experimental observation. This feeling of catching cold often disappeared in 2 or 3 hours.

(9) The common cold was cured relatively easily by the nasopharyngeal treatment.

(10) All children who catch cold easily or those who catch cold all the time, have severe nasopharyngitis and by continuing local treatment of nasopharyngitis, they rarely catch cold or get by with only a slight cold.

(11) Epistaxis is thought to be related to an acute inflammation of the nasal mucous membrane, which follows nasopharyngitis, and can be cured easily by the nasopharyngeal treatment.

From the above facts, the common cold can be thought of as autonomic neurosis caused by acute nasopharyngitis. In fact prolongation of digital pulse wave contraction time or transition of normal to abnormal type blood pressure was observed after the nasopharyngeal stimulation of patients with colds. Local treatment of the nasopharynx is the most effective for the common cold, and the common cold can be prevented in many cases by continuing the nasopharyngeal treatment.

It was often shown that the common cold or influenza was caused by viral infection, and this fact is not inconsistent with nasopharyngitis. It can be thought that acute nasopharyngitis is

were collected and enuresis was cured in all of them after treating the nasopharynx 3 to 5 times. As the nasopharyngeal treatment was continued for 3 to 5 months after enuresis was stopped in these cases, it is not known whether enuresis would have been caused again if the treatment was stopped earlier

8) Pseudomyopia

As it is often said that myopia is due to abnormality of the autonomic nervous system the nasopharyngeal treatment was tried on pseudomyopia in the early stage of myopia Some pseudomyopia progresses to genuine myopia and other cases are cured spontaneously but their distinction between them and only those which become incurable, progress to genuine myopia As one cause of genuine myopia is abnromality of the autonomic nervous system it was not unreasonable to try the nasopharyngeal treatment on it as permanent treatment of abnormality in the autonomic nervous system (Refer to the paragraph on nasopharyngitis and the autonomic nervous system)

When the nasopharyngeal treatment was conducted on children with pseudomyopia the visual power of one child was improved from 0 3 to 0 7 after 2 months The visual power of another child was also improved As the treatment had to be stopped in both cases because of attending school definite results were not known However significant response was observed in 2 cases and this problem has to be studied further

9) Ozostomia (Foetor ex ore)

It was observed in many cases that ozostomia disappeared after the nasopharyngeal treatment. It was probably due to the fact that some of the bacteria which caused nasopharyngitis, had an unpleasant odor and they were removed by the treatment. It was also probable that alveolar pyorrhea aphtha chronic tonsilitis and gastric diseases were improved by the nasopharyngeal treatment and ozostomia was removed secondarily There were actual cases anyhow where an ozostomia was partly removed by the nasopharyngeal treatment

10) Dysosmia

Dysosmia of unknown origins was rarely cured by the nasopharyngeal treatment. In the case over olfactory cleft, dysosmia would be cured with disappearance of inflammation.

11) Common Cold

As studies on influenza made progress and various viruses were discovered the distinction between the common cold and influenza became unclear and a cold was simply concluded to be a viral infection Though it could not be denied that viral infection was a cause of the common cold and influenza there was no explanation for a fundamental question that various symptoms of the so-called common cold were thought due to abnormality of the autonomic nervous system.

When the nasopharynx of a patient with a common cold was observed there existed acute aggravation of nasopharyngitis and this aggravation was improved with recovery from the cold. (On the contrary those in whom acute aggravation of nasopharyngitis was observed did not necessarily have a cold.) It was certain that there was a close relationship between the common cold and acute nasopharyngitis.

Table 69 by KITAMOTO et al (1970) shows general symptoms when influenza was prevalent The relation between nasopharyngitis and symptoms other than cough and sputum shown in this table was mentioned previously in this thesis. Cough and sputum were seen in the case of tracheitis or bronchitis, and most of the patients with acute or chronic tracheitis or bronchitis had severe nasopharyngitis, of which local treatment cured tracheitis in a short term.

In relation between total symptoms of the so-called common cold and nasopharyngitis mentioned above

(1) When the nasopharynx of those with a common cold or influenza was observed, there was always acute aggravation of inflammation.

(2) In the first stage of the common cold, many people complained of abnormal feeling on the dorsal surface of the soft palate (Though this abnormal feeling was often spoken of as an abnormal feeling in the head or throat or as sore throat they did not have much change in oro- and hypopharynx and larynx. When the nasopharynx was examined however severe pain and bleeding were observed and severe inflammation was found in the smears.

Table 69 Subjective symptoms of influenza prevailing in 1950–1957

Year Type / Symptoms	1950 later Type B	1951 winter Type A	1953 winter Type A_1	1957 summer Type A	1957 fall Type B_2
Headache	69*	75*	67*	87*	82*
Cough	6	82	65		66
Sputum	27	28	33	44	30
Myalgia and Arthralgia	16	29	20	25	26
Sore throat	35	38	37	51	48
Nasal occlusion	50	67	39	37	56
Nasal discharge					
Anorexia	32	50	41	86	82
Fatigue	30	45	45	43	32
Epistaxis	6	4	15	12	12
Sweating	—	—	—	63	58

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(6) Open nasal voice, which appears in the first stage of common cold together with an abnormal feeling in the nasopharynx or pharynx (Nasal sounds such as m, n and ŋ twang characteristically) is thought to be Rhinolalia aperta due to slight paresis of the soft palate.

(7) When the nasopharynx of the patients with chronic abnormal feeling of the body was abrased with a cotton swab moistered with 1% $ZnCl_2$ solution, they complained of severe fatigue immediately after the treatment. In the treatment of nasopharyngitis or in the nasopharyngeal stimulation, the patients were attacked by unusual exhaustion and could not even stand up. This was probably related to exhaustion caused by the common cold.

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Dysosmia of unknown origins was rarely cured by the nasopharyngeal treatment In the case where nasopharyngeal inflammation extended over olfactory cleft dysosmia would be cured with disappearance of inflammation

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Table 69. Subjective symptoms of influenza prevailing in 1950–1957

Year Type / Symptoms	1950 winter Type B	1951 winter Type A	1953 winter Type A₁	1957 summer Type A	1957 fall Type B₁
Headache	89*	73*	67*	87%	82*
Cough	76	82	63		66
Sputum	27	28	35	44	38
Myalgia and Arthralgia	16	25	20	25	26
Sore throat	35	36	37	51	48
Nasal occlusion	50	67	59	57	56
Nasal discharge					
Anorexia	32	50	41	86	82
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(7) When the nasopharynx of the patients with chronic abnormal feeling of the body was brushed with a cotton swab moistered with 1% ZnCl solution, they complained of severe fatigue immediately after the treatment. In the treatment of nasopharyngitis or in the nasopharyngeal stimulation, the patients were attacked by unusual exhaustion and could not even stand up. This was probably related to exhaustion caused by the common cold.

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It was often shown that the common cold or influenza was caused by viral infection, and this fact is not inconsistent with nasopharyngitis. It can be thought that acute nasopharyngitis is

caused by viral infection. It should be further studied, however whether the differences in neurotic characteristics, which accompany the common cold are due to virus. The neurosal symptoms of the common cold can be explained simply by acute nasopharyngitis.

6 Conclusion and Summary

The word "nasopharyngeal treatment" was often used in this thesis. By this word it was meant that 1% $ZnCl_2$ solution was applied thoroughly to the nasopharyngeal wall with the aid of a cotton applicator (nasal and pharyngeal cotton applicator).

All the experiments were conducted using only this simple technique. It was not because this technique was the best. The only purpose of this method was to cauterize and to remove the inflammatory part of the nasopharynx with 1% $ZnCl_2$ solution. (The solution was simply used for cauterization of the erosion of the mucous membrane.) Specific action of Zn^{++} or Cl^- was not expected at all. Similar effects were observed using $AgNO_3$, $CuSO_4$ and $ZnSO_4$.

The finding of nasopharyngitis can be done by understanding the relation between nasopharyngitis and various diseases related to nasopharyngitis mentioned in this thesis. Though nasopharyngitis is an easily understandable disease, it becomes difficult to understand when obstructed by old medical knowledge. Most of the diseases related to nasopharyngitis are of unknown origins or are called psychological and incurable. Therefore it is not easy to get an understanding of the relation between nasopharyngitis and these diseases. The nasopharyngeal treatment is not simply a method in otorhinolaryngology but an entirely new theoretical method in medicine.

Special mention must be made that those diseases, which were cured or abated by the nasopharyngeal treatment, were based on clinical experiences of the author.

1. The nasopharyngitis exists ignorantly in many persons.

2. Their existence however may be rarely proved by the routine otolaryngological observations.

3. This may be the reason why nasopharyngitis has not been discussed in the past medicine.

4. The diagnosis of this inflammation is carried out only by the direct abrasion of the nasopharynx mucous membrane.

5. By the local treatment of this nasopharyngitis, following facts are discovered. The treatment of nasopharyngitis causes the improvement of the target diseases.

6. Projection of pain. The nasopharynx wall is not so sensitive for the pain locally but the pain is often projected to the distant area as the dull irritation such as headache. The localization of headache exactly corresponds to the inflammatory part of the nasopharynx wall.

7. The nasopharyngitis exists as the primary area of infection for the inflammation of the distant area, i.e. as the origin of the focal infections, autoimmunizations or collagen diseases like the inflammation of tonsils or others. These facts are certified by the pursuit of progress of the target diseases during the treatment of nasopharyngitis.

8. This pursuit is also effective for the discovery of mechanism of a disease whose origin is not clear.

9. The nasopharynx stimmulation often causes general excitement of the autonomic nervous system. This can be observed through the finger tip plethysmography or the blood pressure change directly after the nasopharynx stimmulation.

10. Nasopharyngitis is often accompanied with autonomic nervous disorders. This can be clarified by the same method as the previous examination in the cases of autonomic nervous disorders.

11. The local treatment of this nasopharyngitis which is accompanied with the autonomic nervous disorders may improve this disorders to be normal, i.e. the autonomic nervous disorders can be controlled by the nasopharynx treatment.

12. Various kinds of uncertain complaints

(so called the diseases of autonomic nervous disorders) are cured by the nasopharynx local treatment

13 The allergic attacks of various kinds are often removed completely by the local treatment of the accompanied nasopharyngitis. This may be due to the sedation of the autonomic nervous excitability which is considered to acceralate the allergic attacks.

14 The nasopharynx stimulation accera lates the alteration of the body fluid. Especially when there exists severe inflammation in the nasopharynx, this phenomenon occurs remarkably

The alteration of eugloblin lysis time (E.L.T.) free fatty acid in the blood and a part of γ-globulin were studied. Also the hormone secretion in the blood was studied. Plasma 11-OHCS (steroid) increases remarkably immediately after the stimmulation of the inflammatory nasopharynx. This fact seems to reveal the mechanism of inflammatory disease a little more precisely

Also the morphological component of the blood alters by the same procedure. Remarkable increase of thrombocytes was observed direct after the abrasion of the inflammatory nasopharynx in a case of the thrombocytopenic purpura. (This case is not yet discribed in this paper.)

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OTO LARYNGOLOGICA

SUPPLEMENT 330

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Papers Dedicated to

Professor Tadashi Fukuda

Upon his Retirement as Director of
the Department of Otolaryngology
Gifu University School of Medicine

EDITORS

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UPPSALA 1975

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Tadashi Fukuda



Tadashi Fukuda

CONTENTS

PREFACE

All papers in this particular issue are dedicated to Professor Tadashi Fukuda by his friends and students to commemorate his retirement as Director of the Department of Otorhinolaryngology Gifu University School of Medicine, Japan, in April, 1974.

Subsequent to his graduation from Kyoto University School of Medicine in 1945, Professor Fukuda initiated his vestibular investigations under Professor Teiji Hoshino who was a real pioneer of neuro-otology in Japan. In 1952 Dr Fukuda was appointed Professor and Chairman of the Department of Otorhinolaryngology Gifu University School of Medicine. Since that time, his research activities have been basically for the investigation of equilibrium function. Professor Fukuda's name is very well known not only within the otological field but also in many related areas for his blind-folded vertical writing test and stepping test which have been extensively utilized by clinicians for the purpose of vestibular examination. His works on the postural reflexes were very well summarized in his masterpiece "Studies on Human Dynamic Postures from the Viewpoint of Postural Reflexes" which was published as a supplementum of the Acta Otolaryngologica in 1961.

In addition to developing his own department extensively Professor Fukuda made a strong effort to create the "Institute of Equilibrium Research" which was established in 1971 to be closely affiliated with Gifu University School of Medicine. Professor Fukuda was named the first director of this important institute. This fact proves that he is such an ambitious scholar in the field of vestibular researches and actually he donated all of himself all of his energies and efforts for the development of equilibrium researches. Furthermore, no one can deny that he is not only a brilliant and imaginative scientist but also a very sensitive humanist and an artist. Presently Professor Fukuda is an honorary member of Japan Society of Equilibrium Research and he is one of its most active members.

Professor Hinoki, Professor Watanabe, and I initiated the collection of commemorative papers and upon our request twenty manuscripts were contributed. I would like to express my sincere appreciation to all contributors for their warm thoughtfulness and friendship which they have shown to Professor Fukuda.

Oct. 16, 1974

Takashi Tokita

Acta Otolaryngol Suppl 330: 9–14 1975

POSTURAL BEHAVIOR AND MOTION SICKNESS[1]

Tadashi Fukuda

From the Department of Otorhinolaryngology Gifu University School of Medicine Gifu, Japan

Abstract. (1) An interesting style of acting was demonstrated on a stage of Kyogen, classic comedy of Japan, titled Funawatashimuko (A boatman and bridegroom in boat" Antagonistic postures which move toward the opposite direction were displayed by boatman who is pulling an oar and passenger who is being moved by the rolling of a boat. (2) Why doesn't one suffer from motion sickness when he drives car but may suffer from it hen he is passenger? This question was answered, from the standpoint of human postures, by observing the antagonistic postures exhibited by bus-driver and passenger and also by the findings in postrotatory eye nystagmus (an indication of artifical motion sickness) which was varied according to the three different positions of the head. (3) Learning postural adjustment against motion sickness, developing through repetitively traveling in vehicles, was also objectively show in posture of an experienced lady bus-conductor hose body inclined in the same direction as that of the driver. Its similarity to the establishment of kinetic labyrinthine reflex in chickens as explained.

Ladies and Gentlemen!

Several years ago, I happened to be watching a very interesting Kyogen (a very old traditional comedy of Japan) entitled Funawatashimuko i.e., A bridegroom and a boatmen in a boat" The comedy was very delightful and it was shown on a New Year s television program. At that time, I had been working on the problem concerning the relation between sea sickness and human postures, and I was deeply impressed by the style in which the actors portrayed the bodily movements of men in a boat, a style of acting which has remained unchanged for 500 years. In order to explain more clearly the relationship between motion sickness and human posture, a demonstration will be given on this stage at the opening ceremony The Shigeyamas, the head family of Kyogen in Kyoto have accepted to perform this comedy much to my pleasure Before the curtain is raised, I would like to emphasize a few important points. Very briefly the story behind this Kyogen goes as follows. A bridegroom is going to visit the parents of his bride and must cross the Biwako Lake in a small boat (like a Venetian gondola) There is a boatman with an oar in his hand waiting on the shore for passengers on his row boat.

A bridegroom who is carrying with him a sealed keg of Sake to be presented to the bride s father hires this boatman. Because the weather is very cold and windy the boatman who is an admirer of Sake (or an elbow bender), repeatedly asks for a cup of Sake. Of course, the bridegroom ignores the request. The boatman is very thirsty and refuses to continue rowing until finally the disgusted bridegroom gives him a cup of Sake by unsealing the keg. As the play continues, the bridegroom who is also an elbow bender becomes thirsty and drinks up all the Sake from the keg with the rather annoyed boatman. The important point which I wish to show and emphasize in this play is each posture of the boatman who is rowing and of the passenger on the boat being moved by rowing. Now let me show you the point by figures!

As you see in Fig. 1 the boatman stretches his upper extremities to push the oar bending forward, his posture inclines to your left. In contrast, the bridegroom inclines in the opposite direction, to your right. Thus the direction

[1] This paper as read at the opening ceremony of the 73rd Congress of Japan Society of Otorhinolaryngology held in Gifu City 1972 by the author ho was the President.

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Fig. 1 The boatman, who is standing, stretches his upper extremities to an oar bending forward and his posture inclines toward your left. On the contrary the sitting bridegroom inclines in the opposite direction, being moved by the roll and his posture inclines toward your right. Thus the directions of postural inclination in a boat are opposite to each other

of inclination of the two postures in the boat are opposite each other As the rowing action continues, the inclination of the posture of the two individuals changes direction as shown in Fig. 2. The boatman who is pulling the oar bends backward, i e., the posture inclines to your right while the posture of the bridegroom inclines toward your left. This alternating pattern of individual posture continues changing rhythmically as the rowing continues. When on the stage, the boatman and the bridegroom move in opposite directions rhythmically the audiences feel just as if they saw a boatman and a passenger in a real boat hurrying its way through the waves of the Biwako Lake The reason why such a realistic impression is imparted by this highly stylized performance of the play can be found in the style of performance in which the postures of the two men incline to the opposite direction alternately a style which has probably been handed down generation after generation Now let us consider the movement of a boat as played in the theatrical performance shown in Figs 1 and 2. The boat is moving straight from the back of the stage toward the audience This movement of the boat is made possible by the work of a boatman who pushes and pulls an oar alternately with a delicate twist of the wrists. As the boat moves forward, it also undergoes a partial rotation (roll) along its longitudinal axis. It must also be noted that the movement of body of the boatman is in the same phase as the longitudinal rotation (roll) of the boat and that of the passenger is in the opposite direction to the rolling movement of the boat. Thus the behavior of the movement of two men in a boat is played in this example from the theatrical performance of a Kyogen play Recently I had a chance to see the staging of one of Japan's modern dances which portrayed the actions of a boatman and a passenger in the same boat. In this play the boatman who was



Fig. 2. As the rowing action continues, the direction of postural inclination changes to the opposite sides. The head and trunk of the boatman who is pulling the oar bends backward, i.e. the posture inclines toward your right, while the bridegroom inclines toward your left. Thus the two postures move into opposite directions.

...wing the boat and the passenger who was ...ing moved by the rolling of the boat, swayed ... the same direction, i.e., both moved to your ...ght or left at the same time. Looking at this ...modern dance, I was impressed by the accuracy ...with which our ancestors had translated a segment ...of real-life behavior to the artificial settings of the ...stage.

Similar contrasts in bodily postures, such as ...hat just illustrated for a boatman and a passen... ...ger can be observed in our daily life. For ex... ...ample, as shown in Fig. 3, the head and trunk of a driver of a bus inclines toward the right when he revolves the handle to his right in order to turn the bus to the right, while the head and trunk of a passenger in the same bus inclines toward the left. Thus, the postures of the two individuals incline in opposite directions. From the viewpoint of centrifugal force, it is interesting to note that the driver deviates across the midline against the centrifugal force, showing a centripetal posture, while the passenger deviates across the midline in the direction opposite to the rotation of the bus, showing a centrifugal posture. Thus opposite postures are clearly evidenced between a driver and passenger in a bus. It is very important to remember that these contrasting postures are not the products of actors on a stage, but are real physiological phenomena caused by the movement of a bus which curves to the right.

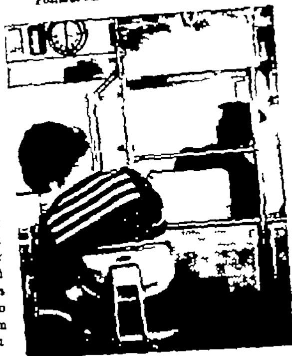


Fig. 3. The head and trunk of the driver of a bus incline toward your right when he revolves the handle in a clockwise direction to make a right turn, while the head and trunk of a passenger in the same bus incline toward your left. Thus the two postures incline toward opposite directions from each other.

The author would like to emphasize that such antagonistic patterns of postures as seen with a driver and a passenger in a moving bus as well as a boatman and a passenger (bridegroom) in a boat on a symbolic stage of Kyogen is deeply related to the cause of motion sickness. A driver as well as a boatman does not normally suffer from motion sickness while a passenger often times does. Moreover, we hear that one does not get motion sickness when he drives a car but when he is in a car as a passenger he does get it. Why is there such a difference concerning motion sickness between a driver and a passenger even though they are in the same car and subject to the same movement? The author would like to demonstrate that the difference is due to the difference in the postures in which the bodies incline in the opposite directions and cross each other by introducing the following observation and experiment.

Güttich (1940) had observed that the position of the eyes and head of a human being is antagonistic in active and passive rotations. When a person begins to rotate around his own long axis, the eyes and the head deviate in the direction of rotation over the midline of the body and continue in this position during the period of the rotation accompanied by eye nystagmus. That is, an active rotation of a person is preceded by the eyes and head which deviate in the direction of rotation. However when a person on a chair is rotated passively the eyes and head *deviate against* the direction of rotation over the midline of the body and continue in this position accompanied by eye nystagmus during the *period* of the rotation, *i.e.*, the eyes and head

remain in the direction opposite the rotation of a chair during a passive rotation Thus, with active rotation, the position of the eyes and head deviates in the direction of the rotation while with a passive rotation it deviates against the direction of the rotation of a chair In this way each position assumes an antagonistic, symmetric posture over the midline of the body

This antagonism is observed not only during rotatory movement around one's own axis but also in other linear and circular movements and it stands as a general rule of postures differentiating active and passive movements of human beings. For example when a runner on a track comes to a curve his posture inclines toward the inside of the curve and he assumes a centripetal posture However as seen in Fig. 3 a passenger who is every inch passively moved in a bus assumes a posture which deviates to the outside of a curve due to the action of the centrifugal force Thus the antagonism of the posture is also evidenced between a runner and a passenger i e between active and passive movements at a curve in human.

It is of interest to examine the posture of the driver in Fig. 3 from the standpoint of the Güttich's observation The driver does not assume a centrifugal posture such as seen in the passenger the driver assumes the same centripetal posture as a runner going around a curve Although the passenger and driver are in the same bus the position of the head and trunk of the former deviates in a direction opposite to the curve while that of the latter deviates in the same direction The two postures incline in opposite directions from each other and assume antagonistic positions. Now returning to why a person when driving a car does not suffer from motion sickness while he may do so when he is a passenger in a car To answer this question the author hypothesized that this is due to the contrast in assumed postures between drivers and passengers. To test this hypothesis the following investigations were performed

Postrotatory nystagmus after 10 rotations in 20 seconds was adopted as an indicator of motion sickness, based on the following theory Postrotatory nystagmus is a phenomenon arising from transient artificial labyrinthine ataxia caused by repeated rotations with which human beings are not familiar Postrotatory sensation is that of vertigo or illusion, i.e a transient motion sickness in which one feels as if still being rotated after the end of the rotation In other words, the rotation test is a method for measuring the time required by a subject on whom unexperienced passive repeated rotations are imposed, to regain almost normal equilibrium of the body after transient labyrinthine ataxia. Postrotatory nystagmus and sensation may be observed as the symptoms of artificial motion sickness which are often accompanied by nausea. So the recorded duration and the number of beats of postrotatory eye nystagmus, serve as an objective index of artificial motion sickness and its magnitude

The chair was designed to turn in a complete circle, in clockwise as well as counter clockwise horizontal direction, and constructed to allow a subject's head to be held in different positions. Seventy healthy adults, male and female without any ear diseases were rotated 10 times in 20 seconds in a counter clockwise direction During rotation the eyes were closed and the head was fixed in 3 different positions as follows first head position normal, i e 30 prone (nose down) position from the German horizontal plane second head position extreme left i e., toward the direction of chair rotation and third head position extreme right, i.e against the rotation of chair In each of the positions, the head was firmly fixed with a band to the head holder attached to the turning chair and the subject was rotated three sequences with 5 minute intervals. Immediately after each rotation the eyes were opened and the examiner calculated the duration and beats of postrotatory nystagmus which showed marked decrease and increase according to the difference of the head position as shown in Fig. 4 In the case of the first head position, i.e., the normal head position the numerical mean value of postrotatory nystagmus for 70 subjects was 27 beats in 21 seconds. With the head positioned in extreme left (the

second head position), it was 21 beats in 16 seconds, and in the third position, against the direction of chair rotation, it was 39 beats in 25 seconds. To summarize, by fixing the head toward the direction of chair rotation (the second head position) the mean value of duration and beats of postrotatory nystagmus decreased markedly compared with the effect of fixing the head in normal head position (the first head position). In contrast, by fixing the head against the direction of chair rotation (the third rotation), it increased markedly.

It is very interesting to examine the results from the viewpoint of Güttich's observation described above that during active rotation the position of the eyes and head deviates toward the direction of rotation, while, during passive rotation, it deviates against the direction of rotation. In the present experiment, each rotation was performed passively by turning a chair. However, the head was fixed in three different positions based on the following assumption. The first head position, which is the normal position of old Barany rotation, was adopted as the standard position. In the second rotation, the head of a passively rotated subject was fixed in the same position as in a subject who turns actively along his own axis. In the third rotation, the head was fixed against the direction of rotation. This is the head position of a subject during passive rotation in a chair in whom the head is not fixed during rotation. For the reason described above, the author would like to call the second head position, the active position of the head, and the third position, the passive position.



Fig. 5. A posture of an experienced lady bus-conductor while the bus is making a right turn. Even being moved passively in a bus, her posture (head and trunk) inclined toward the right, i.e., in the same direction as that of the driver and opposite to that of a passenger shown in Fig. 3.

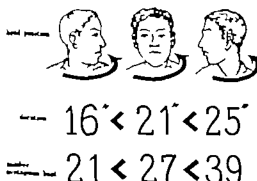


Fig. 4. With head rotated and fixed toward the direction of chair rotation (the second head position), the mean value of duration in seconds and the number of beats of postrotatory nystagmus decreased markedly compared with the case in which the head was fixed in straight head position (the first head position). On the contrary, with head rotated and fixed opposite the direction of chair rotation (the third rotation), it increased markedly. Arrow: direction of chair rotation.

As shown in Fig. 3, the head and trunk of a driver incline toward the right, i.e., toward the direction of the center of the curve and assume a centripetal posture. This posture may be said to correspond with the second head position, i.e., active position of the head resistant to postrotatory nystagmus, namely a posture in which a subject rarely suffers from motion sickness. On the contrary, the head and trunk of a passenger incline toward the left according to centrifugal forces and assumes a posture which is opposite the posture of a driver. The passenger's posture may be said to correspond with the third head position, i.e., passive position of the head

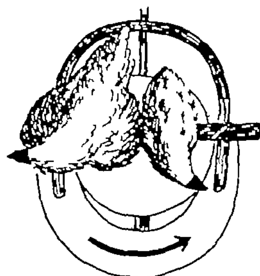


Fig 6 Trained (right) and untrained (left) chickens, 10 seconds after the beginning of rotation. The head of the trained turns in the same direction of rotation through the kinetic labyrinthine reflex, while the head of the un trained deviates still in the opposite direction of rotation by the static labyrinthine reflex (normal deviation).

vulnerable to postrotatory nystagmus, that is a posture in which one easily develops motion sickness. Thus the marked decrease and increase of postrotatory nystagmus observed in the above investigation clearly explains the fact that a subject who is driving a car hardly ever suffers from motion sickness while he easily gets it when he is a passenger in a car

Before summarizing the results, the author would like to add a few comments on the probl em of learned postural adjustment or habitu ation It is widely known that sailors or bus-conductors who have accumulated many years of experience in traveling on vehicles do not suffer from motion sickness. These people have developed special postural habits an example of which is illustrated in Fig 5 The author observed the posture of a trained lady bus-conductor who had been working in a bus for 5 years and made photographs of her back (without her knowl edge) while the bus was turning. When the bus is turned to the right, she assumed a posture with head and trunk inclined toward the right, i e exactly the same direction as the inclination of the driver While being moved passively in the bus, her posture inclined in a direction opposite to that of the passenger shown in Fig.

3 It is very interesting to note that the passenger and lady bus-conductor while sitting on seats in the same bus, took exactly opposite postures and inclined in an opposite direction from each other The lady bus-conductor took a posture similar to that of the driver whose posture was shown to be resistant to motion sickness. Thus a learned postural behavior or habituation is evidenced objectively in a lady bus-conductor who assumed an actively inclined posture toward the center of a curve, i e centripetal posture

This centripetal posture was reported by the author about 20 years ago under the title of Static and Kinetic Labyrinthine Reflex. Func tional development of labyrinthine function with rotatory training" (Fukuda, 1958) To summa rize the principal points shown in Fig. 6 blind folded leghorns were rotated 100 times in 200 seconds to both directions every day for two weeks. It was observed after repeated rotations that the birds, during rotation, turned their heads in the direction of rotation. This pheno-menon was never found in animals before re peated exposures to rotations. The labyrinthine function which caused it has been named the Kinetic labyrinthine reflex In contrast to this terminology the deviation of the head against the direction of rotation has been called the 'Static labyrinthine function a reflex which was called "the normal deviation" to maintain the original position of the head The animal showed a functional progress in equilibrating function through the repeated exposures to ro-tation which were therefore termed training (Fukuda 1963). Thus a learned postural beha vior during rotation was evidenced objectively in the establishment of a kinetic labyrinthine reflex which is here again clearly observed in the posture of a trained lady bus-conductor

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POSITIONAL ALCOHOLIC NYSTAGMUS (PAN) IN MAN FOLLOWING REPEATED ALCOHOL DOSES

Gunnar Aschan and Martin Bergstedt

From the Department of Otolaryngology Regional and University Hospital, Linköping University S eden

Flourens (1842), in animal experiments, and Joffroy & Servaux (1897), in man, showed that among other symptoms alcoholic intoxication brought about a nystagmus. Bárány (1911) and Bárány & Rothfeld (1913) found that this nystagmus was influenced by the position of the head of the test subject. Clinical observations regarding alcoholic nystagmus were made by Frenzel (1939), Plenkers (1943) and Walter (1954).

In a series of experiments on alcoholic intoxication in man, Aschan et al. (1955, 1956), Aschan (1958) and Aschan et al. (1958, 1964) showed that the appearance of PAN followed a very distinct and characteristic pattern. When *a single dose* of alcohol was given, PAN appeared in two phases, PAN I and PAN II separated by an intermediate period. PAN I had a latency of less than half an hour and lasted for 3–4 hours. During this phase the beating direction of the nystagmus was to the right when the head was in the right lateral position, when recorded behind closed eyelids, and to the left when the head was in the left lateral position. The intermediate period followed, in which no nystagmus was observed, and this lasted for 1 2 hours before the second phase began. PAN II thus had a latency time of 5–6 hours from the intake of alcohol. *The direction of PAN II was reversed*, i.e. it beat to the left when the head was in the right lateral position of the head, and vice versa. The duration of PAN II and also the intensity of both PAN I and PAN II were, however proportional to the maximal blood alcohol *concentration and hence to* the amount of alcohol consumed. PAN II always persisted for several hours after all alcohol had disappeared from the blood. Maximal blood alcohol concentrations above 0.25–0 40 per mille were sufficient to produce both phases of PAN. When this concentration was above 0 80 per mille, another type of nystagmus caused by eccentric fixation and *not* by the position of the head, viz. alcohol gaze nystagmus (AGN) was observed (Aschan, 1958).

The results of experiments in patients with unilateral labyrinthine destruction (Aschan et al., 1964) gave the following results

An interaction occurred between an existing vestibular nystagmus of labyrinthine origin and a subsequent PAN caused by alcoholic intoxication. During alcoholic intoxication the two nystagmus phenomena resulted in a manifest nystagmus, which could be described as the algebraic sum of both the intensity and the beating direction of the known pre-experimental vestibular nystagmus and the subsequent PAN This meant *that the resulting nystagmus was* increased when both nystagmus phenomena had the same beating direction and decreased when these directions were opposite. In the latter case an increasing intensity of PAN could either reduce the spontaneous nystagmus to a lower intensity make it disappear completely or even make it change its beating direction.

A closer analysis of the timing of PAN I and

This investigation as supported by the Swedish Medical Research Council, Project 5X 36-03.

PAN II after a single dose of alcohol by correlation to blood alcohol curves obtained in earlier experiments allowed the hypothesis that the appearance of the different phases of PAN were dependent on the rise or fall of the blood alcohol curve

It seemed to be of interest, therefore, to study the PAN phenomena appearing after the administration of repeated alcohol doses, when an interaction between the two nystagmus phenomena PAN I and PAN II was likely to occur

The *aim* of the present investigation was

1 To study the courses of PAN I and PAN II after the administration of *repeated controlled alcohol doses* The PAN observations had to be carefully correlated to the blood alcohol concentration curves.

2. To analyse the possible mechanism of action of the elicitation of PAN phenomena and the interaction between PAN I and PAN II

METHODS

The nystagmus was recorded by the technique described by Aschan (1955) and Aschan et al. (1956) This method for electronystagmography has the advantage that the recordings can be made without fixation, thus eliminating any in*hibition of the vestibular nystagmus by visual* factors. A 10 degree calibration in the plane of the electrodes makes it possible to evaluate not only the beating direction but also the intensity of the nystagmus. Of the parameters obtained, the eye speed in the slow phase of nystagmus has proved to be of most value Its advantages have been demonstrated in the earlier studies both concerning PAN and clinical observations. Besides their documentation value the 30–40 nystagmus records from one experiment of long duration can easily be correlated to the blood alcohol concentration in a single graph At each point of observation recordings were made in the supine, right lateral and left lateral position of the head AGN observations were made only in the supine position with open eyes and 30 eccentric lateral fixation

The blood alcohol concentration was determined by the Widmark micro-method (1932) or by the enzymatic AD-method. Triplicate samples of 0 1 ml blood were withdrawn at intervals of 30–60 minutes. The experimental error of a triplicate sample was ±0 03 per mille[1]

The alcohol whisky administration was varied in order to produce three different types of changes in the blood alcohol concentration

1 *Two single doses* with the second one so arranged in time that it should coincide either with the initial PAN I the intermediate period or a manifest PAN II caused by the first dose. The interval between the two doses thus varied from 4–9 hours The initial dose of whisky varied from 100–200 ml, and the second dose from 50–150 ml.

2. *Repeated small single doses*, to vary the rate and time of absorption Thus 180–540 ml whisky divided in 8–18 doses were given over a period of 3–6 hours.

3 A moderate dose followed by small doses, in an attempt to *maintain a constant blood alcohol level* over a fairly long period of time. Following a primary dose of 120–140 ml whisky 330–440 ml divided in 21–25 doses of 10–30 ml each were given over a period of 9–11 hours.

Experiments with one single dose in test subjects used in previous investigations served as a pilot study Experiments with alcohol intake over such long periods as 11 hours or more could not be carried through without giving some food thus introducing factors which influenced the alcohol absorption

MATERIAL AND PROCEDURE

The test subjects were healthy females and males with moderate drinking habits. The age distribution was 19–31 years. In all subjects the neuro-otological findings, including pure tone audiograms, were normal. Many of the subjects had participated in earlier single dose experiments. A total of 43 experiments were performed on 38 test subjects. Each experiment started early

1 per mille = 1 mg/g = 0.1 per cent 100 mg = 0.022 moles alcohol/l.

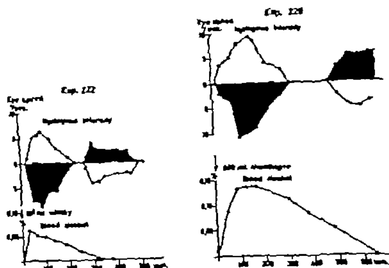


Fig. 1. Experiment 222 and 226. Blood alcohol curves and PAN observations after single doses of alcohol. In experiment 222 with plain whisky the blood alcohol curve has a marked peak, whereas the diluted alcohol in experiment 226 gives slow change-over from rising to falling blood alcohol. In the nystagmus intensity diagram the observations from the right lateral position of the head are above the zeroline, those from the left lateral position below. White areas right beating nystagmus, black areas left beating. Thus PAN I = white over black areas, and PAN II = black over white areas.

in the morning, no food having been taken since the previous night. During the 10–26 hours that the experiment lasted, repeated tests for PAN and blood alcohol were carried out at intervals of 30–60 minutes. The results given in this communication are based on over 3 000 separate nystagmus recordings and 4 000 blood alcohol tests.

RESULTS

. One single dose

I an introduction the two experiments in Fig. are presented. They are taken from other nvestigations but will serve as a guide for the ubsequent figures. Both refer to single doses f alcohol. In experiment 222, 120 ml whisky nd in experiment 226 half a litre of champagne vas consumed within 15 minutes. In both experiments the two phases of PAN are easy to recognize and to correlate to the blood alcohol curves. The stronger liquor in experiment 22. compared with the diluted alcohol given as champagne in experiment 226 results in quite different blood alcohol curves especially regarding the change-over from increasing to falling blood acohol concentration. In experiment 222 the curve shows a pronounced peak, whereas in experiment 226 the change is more gradual. Although the present investigation was restricted to pure whisky some of the test subjects could only take the whisky diluted with some water which was immediately reflected in the blood alcohol curves. For example the peak from the blood alcohol curve of experiment 222, Fig. 1 expected in two single dose experiments, is missing in experiments 171 152 and 95 (Figs. 3, 5 and 2 respectively). Here the diluted whisky gives curves which are more similar to that for champagne.

B. Two single doses

A total of 20 experiments of this type were carried out. The two doses will be referred to as primary and secondary as also will the different phases of PAN that could be attributed to a particular dose. *The primary dose* varied *from 100–200 ml whisky and the secondary from 50–150 ml.* The intake of the secondary dose was timed according to the primary PAN phenomena observed *so that it would interfere*

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PAN II after a single dose of alcohol by correlation to blood alcohol curves obtained in earlier experiments allowed the hypothesis that the appearance of the different phases of PAN were dependent on the rise or fall of the blood alcohol curve

It seemed to be of interest, therefore to study the PAN phenomena appearing after the administration of repeated alcohol doses, when an interaction between the two nystagmus phenomena PAN I and PAN II was likely to occur

The *aim* of the present investigation was

1 To study the courses of PAN I and PAN II after the administration of *repeated controlled alcohol doses* The PAN observations had to be carefully correlated to the blood alcohol concentration curves.

2. To analyse the possible mechanism of action of the elicitation of PAN phenomena and the interaction between PAN I and PAN II

METHODS

The nystagmus was recorded by the technique described by Aschan (1955) and Aschan et al. (1956) This method for electronystagmography has the advantage that the recordings can be made without fixation thus eliminating any inhibition of the vestibular nystagmus by visual factors. A 10 degree calibration in the plane of the electrodes makes it possible to evaluate not only the beating direction but also the intensity of the nystagmus. Of the parameters obtained, the eye speed in the slow phase of nystagmus has proved to be of most value Its advantages have been demonstrated in the earlier studies both concerning PAN and clinical observations. Besides their documentation value the 30–40 nystagmus records from one experiment of long duration can easily be correlated to the blood alcohol concentration in a single graph At each point of observation recordings were made in the supine right lateral and left lateral position of the head. AGN observations were made only in the supine position with open eyes and 30 eccentric lateral fixation

The blood alcohol concentration was determined by the Widmark micro-method (1932) or by the enzymatic AD-method. Triplicate samples of 0 1 ml blood were withdrawn at intervals of 30–60 minutes. The experimental error of a triplicate sample was ±0 03 per mille [1]

The alcohol whisky administration was varied in order to produce three different types of changes in the blood alcohol concentration

1 *Two single doses* with the second one so arranged in time that it should coincide either with the initial PAN I the intermediate period or a manifest PAN II caused by the first dose The interval between the two doses thus varied from 4–9 hours. The initial dose of whisky varied from 100–200 ml, and the second dose from 50–150 ml.

2. *Repeated small single doses* to vary the rate and time of absorption Thus 180–540 ml whisky divided in 8–18 doses were given over a period of 3–6 hours.

3 A moderate dose followed by small doses, in an attempt to *maintain a constant blood alcohol level* over a fairly long period of time. Following a primary dose of 120–140 ml whisky 330–440 ml divided in 21–25 doses of 10–30 ml each were given over a period of 9–11 hours.

Experiments with one single dose in test subjects used in previous investigations served as a "pilot study Experiments with alcohol intake over such long periods as 11 hours or more could not be carried through without giving some food thus introducing factors which influenced the alcohol absorption

MATERIAL AND PROCEDURE

The test subjects were healthy females and males with moderate drinking habits. The age distribution was 19–31 years In all subjects the neuro-otological findings, including pure tone audiograms, were normal Many of the subjects had participated in earlier single dose experiments. A total of 43 experiments were performed on 38 test subjects. Each experiment started early

1 per mille = 1 mg/g = 0.1 per cent = 100 mg ~ 0 0... moles alcohol/l.

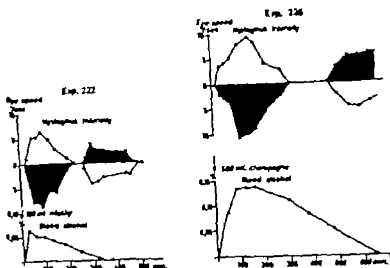


Fig. 1. Experiment 222 and 226. Blood alcohol curves and PAN observations after single doses of alcohol. In experiment 222 with plain whisky the blood alcohol curve has a marked peak, whereas the diluted alcohol in experiment 226 gives a slow change-over from rising to falling blood alcohol. In the nystagmus intensity diagram the observations from the right lateral position of the head are above the zeroline, those from the left lateral position below. White areas right beating nystagmus, black areas left beating. Thus PAN I = white over black areas, and PAN II = black over white areas.

in the morning, no food having been taken since the previous night. During the 10–26 hours that the experiment lasted, repeated tests for PAN and blood alcohol were carried out at intervals of 30–60 minutes. The results given in this communication are based on over 3 000 separate nystagmus recordings and 4 000 blood alcohol tests.

RESULTS

A. *One single dose*

As an introduction the two experiments in Fig. 1 are presented. They are taken from other investigations but will serve as a guide for the subsequent figures. Both refer to single doses of alcohol. In experiment 222, 120 ml whisky and in experiment 226 half a litre of champagne was consumed within 15 minutes. In both experiments the two phases of PAN are easy to recognize and to correlate to the blood alcohol curves. The stronger liquor in experiment 222 compared with the diluted alcohol given as champagne in experiment 226 results in quite different blood alcohol curves especially regarding the change-over from increasing to falling blood alcohol concentration. In experiment 222 the curve shows a pronounced peak, whereas in experiment 226 the change is more gradual. Although the present investigation was restricted to pure whisky some of the test subjects could only take the whisky diluted with some water which was immediately reflected in the blood alcohol curves. For example the peak from the blood alcohol curve of experiment 222, Fig. 1 expected in two single dose experiments, is missing in experiments 171 182 and 95 (Figs. 3, 5 and 2 respectively). Here the diluted whisky gives curves which are more similar to that for champagne.

B. *Two single doses*

A total of 20 experiments of this type were carried out. The two doses will be referred to as primary and secondary as also will the different phases of PAN that could be attributed to a particular dose. The primary dose varied from 100–200 ml whisky and the secondary from 50–150 ml. The intake of the secondary dose was timed according to the primary PAN phenomena observed so that it would interfere

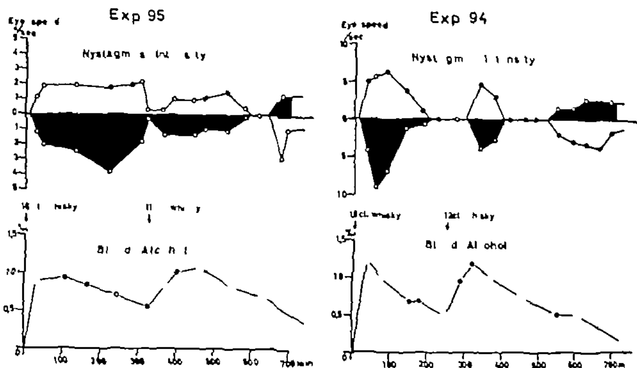


Fig 2 Two single doses of whisky In experiment 95 the *second dose was given at the end of a manifest PAN I* Despite the higher secondary blood alcohol maximum the last—secondary—part of PAN I has a shorter duration and a lower intensity In experiment 94 the second dose is timed to coincide with the primary intermediate *period. Despite the same secondary blood alcohol maximum* the secondary PAN I is shorter and of a lower intensity than the primary PAN I

(1) with the primary PAN I (2) with the primary intermediate period or (3) with an already manifest primary PAN II Thus there was a systematic increase from 4 to 9 hours in the interval between the intake of the two doses, this interval being adjusted according to the primary nystagmus observations in each experiment and to the desired point of interference of the three alternatives mentioned above

(1) A typical example of administration of the secondary dose just before the end of primary PAN I is illustrated in Fig. 2, experiment 95 The primary PAN I was very near to an end when the secondary dose elicited a secondary PAN I On comparing the primary and secondary PAN I it is seen that the secondary PAN I has a somewhat shorter duration and also a lower intensity than the primary The blood alcohol curve shows a higher secondary maximum. *Only the first part of a PAN II was recorded*, but this appeared when the blood alcohol was decreasing.

(2) Administration of a secondary dose during the primary intermediate period is illustrated in Fig. 2, experiment 94 Here two separate PAN I were observed. In this experiment also the *shorter duration of the secondary PAN I compared* with the primary is observed and here the reduction is more marked The intensity of the secondary PAN I is also lower than that of the primary despite the maximal blood alcohol concentration in the secondary peak. The duration of the secondary intermediate period was two hours PAN II appears, as in all experiments, *with the final fall in the blood concentration* The differences in the time of appearance of the primary phenomena and the necessity for adjusting the interval between the doses individually in each experiment are also clear on comparing the two experiments in Fig 2

(3) Typical examples of a secondary dose given during a manifest primary PAN II are given in Fig. 3 experiments 171 and 172. In both experiments the secondary dose was about 1 3 of the primary one Here the primary PAN observations were within the limits observed in earlier

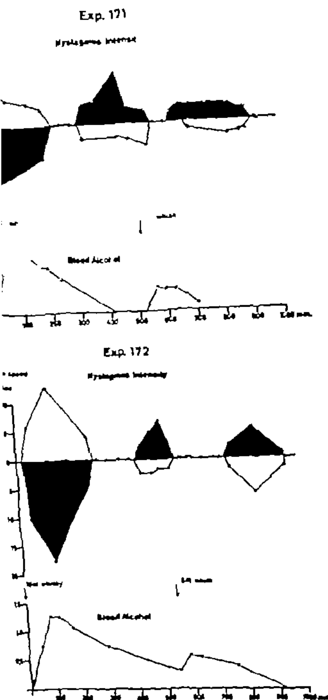


Fig. 3. Two single doses of whisky. The second dose is timed to coincide with a manifest primary PAN II, and in both experiment 171 and 172 this results in blocking of PAN for 1 hour and 3 hours respectively.

single dose experiments just until the secondary dose was taken. The secondary dose in both experiments resulted in a disappearance of the primary PAN II, in experiment 171 for a short period, and in experiment 172 for a longer period. This "blocking" of the primary PAN II by a secondary PAN I must have its explanation in the fact that the two have opposite beating

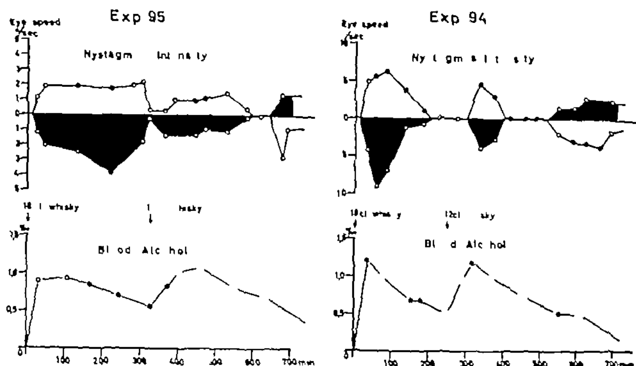


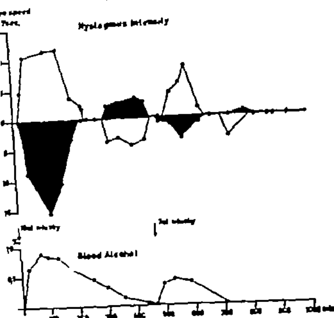
Fig 2. Two single doses of whisky In experiment 95 the second dose was given at the end of a manifest PAN I Despite the higher secondary blood alcohol maximum the last—secondary—part of PAN I has a shorter duration and a lower intensity In experiment 94 the second dose is timed to coincide with the primary intermediate period. Despite the same secondary blood alcohol maximum the secondary PAN I is shorter and of a lower intensity than the primary PAN I

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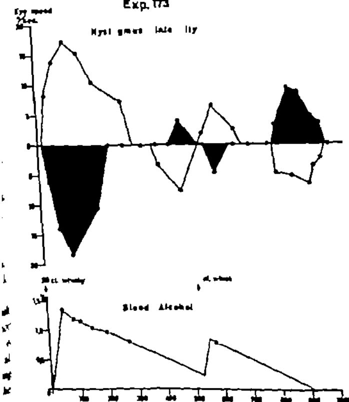


Fig. 5. Two further single dose experiments (182 and 173) with the same test subjects as in Fig. 3 (experiments 171 and 172, respectively). The comparatively higher secondary dose in both these experiments than in experiments 171 and 172 results in a secondary PAN I of a higher intensity and under these experimental conditions this results in a reversed beating direction of PAN over period of about 2 hours. With more frequent observations during the critical stage, an intermediate period is also observed.

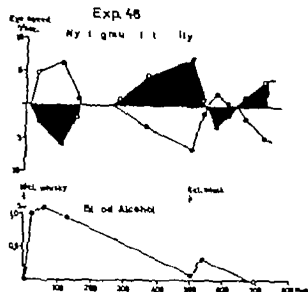


Fig 4 Experiment 46. Two single doses of whisky the second timed to coincide with a primary PAN II. In this test subject the second dose resulted in such an intense secondary PAN I that for about one hour not only was there blocking of PAN but also a change in beating direction.

directions. The two experiments 171 and 172 also confirm another earlier observation that the intensity of PAN I is dependent on the degree of alcoholic intoxication This is evident in the first part of the experiments. In experiment 171 the primary maximal blood alcohol concentration was 1 0 per mille, and in experiment 172, 1.35 per mille. As a result the primary PAN I in experiment 172 has a much higher intensity than that in experiment 171 This is also valid for the secondary PAN I. Thus, in experiment 171 a secondary blood alcohol maximum of 0 4 per mille resulted in blockade of the primary PAN II for 1 hour whereas in experiment 172 the higher secondary maximum of 0 6 per mille gave a block that lasted for 3 hours.

A third example of a secondary dose 1/3 of the first one, is illustrated in experiment 46, Fig. 4 Here the secondary dose gave a secondary blood alcohol maximum of 0.32 per mille In *this test subject*, however this dose was sufficient not only to block the primary PAN II but also to reverse its beating direction for a short period.

A quantitative factor regarding the intensity of the primary PAN was found on analysis in earlier experiments. In the experiments in Fig 3 and 4 this also seems to be valid for the secondary *PAN* phenomena, but because of the individual variations illustrated, with blocking alone of the primary PAN II in Fig. 3 and blocking combined with reversal of the beating direction in Fig. 4 we repeated the tests in the same test subjects.

Experiments 173 and 182 in Fig. 5 refer to the same test subjects as in experiments 172 and 171 (Fig. 3) respectively The principal change in the experimental conditions in Fig. 5 was that the secondary dose was kept higher in relation to the primary dose. This resulted in a secondary PAN I of a higher intensity and as a result the intensity of the secondary PAN I was higher for a period of about 2 hours than that of the primary PAN II Thus the primary PAN II not only disappears but also changes beating direction. The more frequent observations also showed a short interval without nystagmus—an interval during which the primary PAN II and the secondary PAN I were obviously of the same intensity and thus blocked each other

Figs. 3–5 are representative of the other experiments. They also show the individual *variations* which complicate statistical treatment of the material as a whole, the reason for which the results are documented in this way It is also worthy of observation that the way in which the whisky is taken influences the blood alcohol curve. Thus experiments 172 and 173 represent whisky taken undiluted, with peaks in the curves, and experiments 171 and 182 whisky taken diluted with water showing a slow change-over from rising to falling blood alcohol concentrations.

It is concluded that a quantitative factor exists in this type of experiment also A low secondary dose has only a blocking action on the primary PAN II while a higher dose results in a change in the beating direction over a short (exp 46) or long (exp 173 and 182) period of time Thus the results obtained by Aschan et al (1956) with single dose experiments, showing that the degree of intoxication influences the intensity of PAN I but not the duration, ha

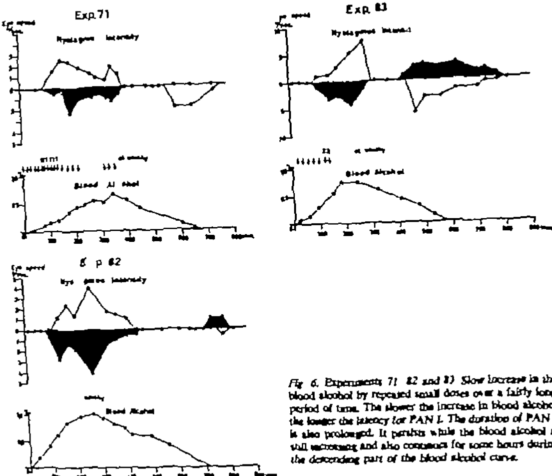


Fig. 6. Experiments 71, 82 and 83. Slow increase in the blood alcohol by repeated small doses over a fairly long period of time. The slower the increase in blood alcohol the longer the latency for PAN I. The duration of PAN I is also prolonged. It persists while the blood alcohol is still increasing and also continues for some hours during the descending part of the blood alcohol curve.

appeared, as the test subjects refused to participate any longer.

A reversed form of alcohol administration, i.e. small doses followed by a larger one, is illustrated in Fig. 7 (experiment 93). Seven 30 ml doses of whisky given over a period of 2 1/2 hours gave a slowly rising curve with a blood alcohol maximum of 0.85 per mille after 3 hours. As in previous experiments, this caused a PAN I with a prolonged duration. A further single dose of 120 ml whisky at 5 hours induced a new rise in the blood alcohol to a maximum of 1.31 *per mille*. This caused a secondary PAN I of a rather short duration, a new and prolonged intermediate period lasting for 2 1/2 hours, and finally a PAN II with a latency of 9 1/2 hours and still persisting when the experiment was discontinued.

In principle the PAN findings in experiment 93, Fig. 7 are similar to those illustrated in experiment 94, Fig. 2. There are differences in intensity and timing, but the corresponding blood alcohol curves are similar in that they both show two blood alcohol maxima separated by a fall in concentration.

"Constant" blood alcohol levels

It was the aim of these experiments to produce a certain moderate blood alcohol level by giving the test subject an initial large dose of alcohol, and then to maintain this level by repeated small doses. In all eight experiments with an initial dose of 120–140 ml whisky followed by 10–25 doses of 10 ml occasionally 20 ml and sometimes an extra dose of 30 ml over a time of 8 1/2–10 1/2

proved valid even in this more complex experimental situation

Unfortunately these long experiments were rather tiring for the test subjects, and it was not always easy to persuade them to return for further experiments. This explains why some of the experiments were not carried to the absolute end of PAN II At the end of some long experiments we has difficulties in keeping the test subjects awake. Thus sleepiness sometimes resulted in poor recording at the end of PAN II and we would like to point out that this part of PAN II includes experimental errors and cannot always be assumed to be accurate in some of these experiments.

Repeated small doses

In previous investigations and in the experiments hitherto described in this study the alcohol intake started with a large dose. The result was a rapid rise in the blood alcohol concentration and the mean value for latency for PAN I was about 30 minutes. As the PAN findings seem to be closely related to the blood alcohol curves, the first problem was to determine whether and if so how a slow rise in the blood alcohol concentration influenced PAN

Repeated small doses of alcohol were given to 16 test subjects. Ten to eighteen 10–30 ml doses of whisky were given over a period of 3–5 hours. As seen from the graphs in Fig. 6 the doses given in experiments 71 82 and 83 chosen for illustrating the result brought about a slowly rising blood alcohol curve the maximum occurring after 3–6 hours, compared with 1/2–2 hours with larger single doses.

The latency for PAN I was prolonged in all these experiments. The slower the increase in the blood alcohol curve the longer the latency for PAN I the longest latency observed being 2 hours. On the other hand although the latency was delayed, PAN I appeared at blood alcohol concentrations as low as 0.1 per mille

It was anticipated that the slow absorption of alcohol with this type of administration would give this result Thus it seemed justified to check the conditions on the quickest possible increase in blood alcohol, i e. by intravenous administration

Three patients were given a solution of 10 g alcohol per 1000 ml intravenously in a dose of 100 ml per 5 minutes. All three patients had a manifest PAN I after $8^1/_2$ minutes. Clinical experience with alcohol blockade (80 volumes per cent) for neuralgia has shown in every case tested (18 cases) a typical PAN I within 10 minutes.

The duration of PAN I was also prolonged, as seen for example in Fig. 6 (experiments 82 and 71) This duration was now $6–7^1/_2$ hours, compared with 3–4 hours after a single dose.

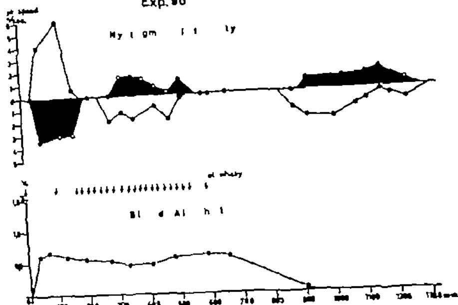
The intermediate period was prolonged lasting for 2–4 hours compared with 1–2 hours after single doses, and started later as a result of the increased duration of PAN I and the prolonged latency for that phenomenon.

As a consequence of the observations just mentioned the latency of PAN II was prolonged. As expected, PAN II lasted in every case for several hours after the blood alcohol had returned to zero In the experiments presented in Fig. 6 PAN II stopped after 13–14 hours, whereas the blood alcohol had returned to zero after $9^1/_2$–12 hours.

For ethical reasons the increase of blood alcohol could not be carried above certain limits. However the results obtained, with a slow change-over from a rising to a falling blood alcohol concentration as late as 6 hours after the start of the experiments seem to have given us the information required.

Combined large and repeated small doses

Fig. 7 illustrates an experiment of this type (experiment 58) with the blood alcohol concentration increasing to a comparatively high value the maximum being 1 50 per mille after $5^1/_2$ hours. This increase resulted in a PAN I with a short latency but a duration of $7^1/_2$ hours, the duration showing essentially the same pattern as after the intake of repeated small doses as illustrated in Fig. 6. Experiment 58 had to be discontinued after $9^1/_2$ hours before PAN II



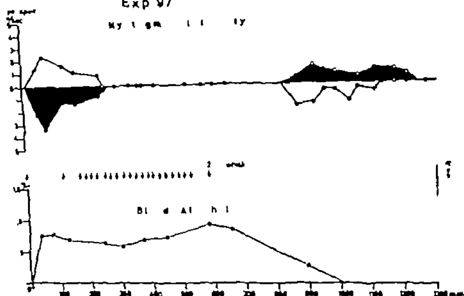


Fig. 8. Experiments 96 and 97. An attempt at producing "constant" blood alcohol levels. The latency, intensity and duration of PAN I are just as in the single dose experiments. Despite the attempt at constancy the blood alcohol curves still show two separate maxima. As result in experiment 96 the secondary maximum gives a secondary PAN I which blocks an already manifest primary PAN II. In experiment 97 the increase in blood alcohol concentration appears earlier and is rather more marked. Hence the primary PAN II and the secondary PAN I block each other for about 10 hours.

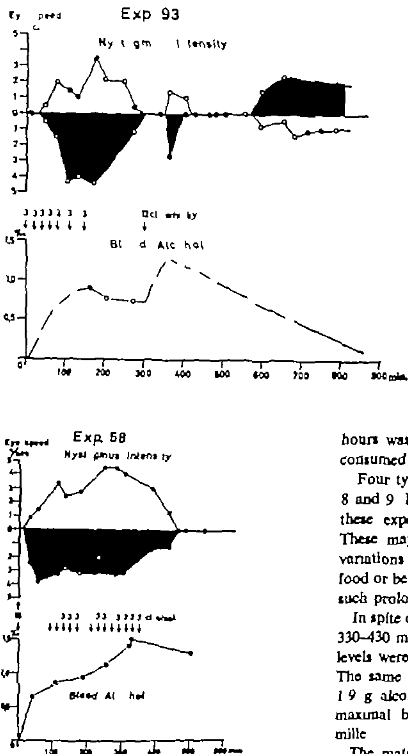


Fig 7 Experiment 58 shows an increasing blood alcohol concentration over a period of 5½ hours. Despite the irregular alcohol intake the prolonged ascension of the blood alcohol curve explains the short latency the long duration of PAN I and the intensity In experiment 93 the irregular alcohol intake results in a blood alcohol curve with two separated maxima. The secondary maximum coincides with a *primary intermediate period* and consequently the PAN findings, with a primary and secondary PAN I, are in principle the same as in Fig 2 (Experiment 94).

hours was given The total amount of whisky consumed thus ranged from 330–430 ml

Four typical examples are illustrated in Figs. 8 and 9 However the blood alcohol curves in these experiments all show slight variations These may be partly explained by individual variations in rate of absorption or intake of food or beverage which had to take place during such prolonged experiments.

In spite of the large doses of alcohol given, i e 330–430 ml whisky the maximal blood alcohol levels were no higher than 0 45–0.95 per mille. The same amounts given as single doses, 1 6–1 9 g alcohol *per kilo*, would have produced maximal blood alcohol levels of 2.3–2.6 per mille

The material can be divided into two main groups, one *with a rapid initial rise in blood alcohol concentration and a second with a slower* rise caused by dilution of the whisky with water

Fig. 8 (experiments 96 and 97) illustrates two typical examples of a rapid initial increase in the blood alcohol concentration with a first *maximum occurring in* ~100 *minutes. As ex*pected, this resulted in a PAN I appearing with the usual latency of about 30 minutes. In experi

way as after a single dose of alcohol, but its duration was slightly above the mean in single dose experiments. The intermediate period here, however lasted for 9 hours and was followed by a PAN II *which disappeared* 4 hours after the blood alcohol had returned to zero.

The PAN observations in experiment 96 (Fig. 8) were in principle the same as those in experiments 171 and 172, illustrated in Fig. 3. In these latter experiments the blood alcohol curve showed two very pronounced maxima. The blood alcohol curves in experiments 96 and 97 also showed the two maxima, but here they are much less *distinct* than in the two large dose experiments.

Thus the explanation for the PAN findings in experiment 96 would seem to be that the secondary maximum in the blood alcohol curve results in a secondary PAN I during an already present primary PAN II. As the two nystagmus phenomena have opposite beating directions, this means that they level out each other

In experiment 97 the secondary maximum in the blood alcohol is reached at 10 hours after a slow secondary rise in the blood alcohol curve which starts as early as at 5 hours. According to the results already illustrated in Fig. 6, this slow increase in the blood alcohol over a period of 5 hours should result in a prolonged PAN I. The primary PAN II and the secondary PAN I due to the rise in blood alcohol from 5–10 hours also have opposite beating directions. Obviously they must have about the same intensity and consequently they level out each other The prolonged PAN I observed on continuous rise in blood alcohol over a long period of time, combined with an ordinary intermediate period, explains why in experiment 97 no PAN is recorded over a period of 9 hours.

Experiments 64 and 67 (Fig. 9) show a comparatively slow rise in the first part of the blood *alcohol curve despite the larger initial dose. As* a result the latency for PAN I is slightly above the a erage in both experiments.

In experiment 64 the maximum in the blood alcohol concentration curve is delayed and the first slight fall is seen after 6 hours. This explains the long duration of PAN I which ends at 9 hours. A second hardly noticeable rise in the blood alcohol at 11 hours gives a *prolonged intermediate* period of about 3 hours, after which PAN II starts and persists for more than two hours after the blood alcohol has returned to zero.

PAN I *is also prolonged in experiment* 67 but not as greatly as in experiment 64 Here the first maximum in the blood alcohol curve also occurs earlier After an intermediate period PAN II starts in the left lateral position and then disappears again. *This must result from the* secondary rise in the blood alcohol concentration with a second maximum at 8 hours. Even such a very slight rise seems to be enough to produce a secondary *PAN I* which levels out the primary PAN II for three hours. PAN II then persists for 5 hours after the blood alcohol has returned to zero

As can be seen in Fig. 8 and 9 the PAN find*ings in this last group of experiments vary some*what. In all of them, however it may be said that the blood alcohol curves give a key which explains the differences in PAN The occurrence *of different* blood alcohol maxima, especially and even increases in the blood alcohol of only 0.1–0.2 per mille over several hours are sufficient to cause interactions between the secondary PAN I and primary *PAN II* phenomena. Thus all results of this kind can be explained by correlating the PAN findings *with the* blood alcohol curves. It may be worth stressing that *PAN I always* appeared at the start of the ex*periment and that all experiments* ended with *a* PAN II lasting for a considerable length *of* time after the blood alcohol had returned to zero.

DISCUSSION AND CONCLUSION

In the introduction the standard values obtained *in earlier investigations* on PAN after single *doses* were given *(Aschan, Bergstedt, Goldberg & Laurell, 1956)*. The interaction between spontaneous vestibular nystagmus and PAN was also described in detail (Aschan, Bergstedt &

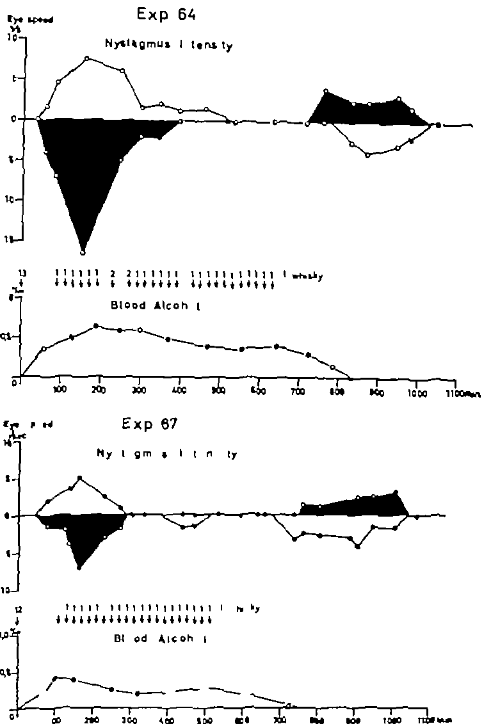


Fig 9 Experiments 64 and 67 both show a slow rise in the blood alcohol curve, resulting in prolonged latency for PAN I In experiment 64 the late primary blood alcohol maximum gives prolongation of PAN I and the secondary ha dly noticeable rise gives a prolonged nter mediate period. In experiment 67 the first blood alcohol maximum appears earlier than in experiment 64 thus the duration of PAN I is shorter The slightly pronounced secondary blood alcohol maximum in experiment 67 occurs just after the first appearance of the primary PAN II, with consequent blocking of the two PAN phases for nearly three hours, the result being a secondary inter mediate period. Note the long duration of PAN II in both Figs. 8 and 9 after the blood alcohol has returned to zero

ment 96 this PAN I lasted for the usual length of time and after a normal intermediate period PAN II appeared. This PAN II ended at about $9^1/_2$ hours and for a period of nearly 5 hours no PAN was observed. After this a secondary PAN II was manifest, and persisted about 6 hours after the blood alcohol had returned to zero

In experiment 97 PAN I appeared in the same

the last drink. Last but not least, the intermediate period reduces the possibilities of using PAN tests for routine medico-legal purposes, but under certain circumstances and with the essential reservation that nystagmography behind closed eyelids is used, it can be a complement to blood and urine alcohol analyses.

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Goldberg, 1964) In these latter studies a quantitative factor—the degree of intoxication—was very marked As anticipated, a similar interaction between the two phases of PAN with their reversed beating directions was also found in this investigation

In the present experiments with multiple alcohol intake changes of various kinds in the course of the blood alcohol curves were observed All nystagmus observations in this investigation were correlated with the blood alcohol curves this close analysis of the material allowed the following conclusions

(1) The latency of PAN I depends on the rate of the initial blood alcohol rise. If the absorption of alcohol is very slow and consequently the increase in blood alcohol is also slow the latency time for PAN I may be as long as 2 hours.

In such experiments PAN I also appears at blood alcohol concentrations as low as 0 1 per mille. If on the other hand, the usual means of absorption is eliminated by injecting alcohol, the latency time can be reduced to $8^1/_2$–10 minutes.

(2) A *rising* blood alcohol induces a PAN I whose duration covers that period of time in which the blood alcohol is increasing, the subsequent blood alcohol maximum and at least 2 hours into the descending part of the curve Even such a low increase as 0 1–0.2 per mille over several hours causes a PAN I independent of where in the blood alcohol curve this rise occurs.

(3) A *falling* blood alcohol induces a PAN II after a latency time of at least 3 hours after the change-over from an ascending to a descending blood alcohol curve

(4) PAN II always lasted for several hours after the blood alcohol had returned to zero. The long duration of PAN II in the last group of experiments (up to 440 ml whisky over a period of $10^1/_2$ hours) confirms earlier observations that the duration of PAN II is dependent on the degree of intoxication even when the doses are spread out over such a long period!

(5) The *degree of intoxication* has marked influence on the intensity of PAN I This is valid not only for a primary PAN I but also for a secondary PAN II as shown especially in repeated two-dose experiments in the same test subject.

(6) Alcohol-induced positional nystagmus, whether PAN I or PAN II will always interact with each other when, as a result of repeated doses of alcohol, they are timed to coincide. This timing will depend on repetition of a rising and falling blood alcohol in the same blood alcohol curve On the basis of the resulting PAN the time schedule obtained in our single dose experiments was proved valid in this investigation also

(7) The resulting nystagmus phenomena will always be the algebraic sum of the beating direction and intensity of the two simultaneously present PAN at any given time point. Hence the parallelism with the interaction and resulting nystagmus described in the introduction between spontaneous vestibular nystagmus following labyrinthine destruction and PAN

These conclusions may be of value from some practical clinical or medico-legal aspects.

Blood alcohol concentrations as low as 0.1 per mille cause a positional nystagmus with an intensity and a beating direction what in clinical neuro-otological practice may lead to suspicion of severe neurological disturbances, particularly in the posterior fossa. Even rather moderate alcoholic intoxications, which may be easily overlooked, can be clinically misleading. Repetition of the tests—obviously without alcohol intake—after a few hours will answer this question Frenzel (1939) gave an example of the clinical errors that may result from PAN and this seems worth pointing out once more

The presence of both AGN and a PAN I or II should indicate a blood alcohol concentration above 0 8 per mille In the clinic this should not present difficulties in differential diagnosis, but from a medico-legal aspect it may be of value

The presence of PAN I may show that alcohol must have been consumed within the last 4 hours. A PAN II on the other hand usually indicates that several hours have elapsed since

the last drink. Last but not least, the intermediate period reduces the possibilities of using PAN tests for routine medico-legal purposes, but under certain circumstances and with the essential reservation that nystagmography behind closed eyelids is used, it can be a complement to blood and urine alcohol analyses.

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Table I. *Similarities between O.K.N. and F.I.N.*

1. Response build up and occurrence for entire period of stimulation
2. No habituation
3. Afternystagmus in same direction
4. Occasional after-afternystagmus in opposite direction
5. Frequency spectrum as function of stimulus temporal frequency
6. Mean peak frequency (2.0–3 beats/sec)
7. Existence of lower and upper frequency thresholds

labyrinths. In all cases, testing sessions started 30 *minutes* after intramuscular injection of amphetamine sulfate (1 mg/kg of body weight) which was given to obtain reliable and stable levels of alertness. Stimulation was carried out under binocular or monocular conditions. In the latter case, an opaque sclerocorneal contact occluder was utilized in order not to interfere with the eye movements. In some experiments, the position of the monkey in space was varied by tilting in the frontal plane (roll angles) and/or placing the animal in the prone and supine positions (pitch angles).

The techniques for stimulation and recording have been described in detail in the earlier publications. In short, O.K.N. was induced by moving luminous stripes on a rear projection screen. The chosen stimulus parameters were a period of 64° at the center of the screen with a light/dark ratio of 1:9, four such periods being present on the screen at any one time. Stimulus temporal frequencies varied from 0.03 to 32 Hz and the *mean luminance of the light bars measured* from 0.82 log ftL to 7.73 log ftL. F.I.N. was elicited with a Grass PS2 photostimulator. The flicker frequency varied from 1 to 35 Hz; the flash duration was approximately 10 μsec at a luminous intensity of 3.87 × 10⁴ candles. Recording of eye movements was made with conventional AC electro-oculography. The method which has been described in detail in previous communications (Pasik et al., 1971; Pasik et al., 1973), allowed the identification of 8 vectors of rapid eye movements with respect to the head, namely upward, downward, to the right, to the left, and the four intermediate obliques.

The surgical techniques involved the section of the optic chiasm in the midsagittal plane (Pasik & Pasik, 1972) and/or the destruction of the labyrinths and section of the 8th nerves (Pasik & Pasik, 1973).

RESULTS AND DISCUSSION

Similarities between O.K.N. and F.I.N.

The characteristics common to both phenomena are summarized in Table I. Under proper conditions of alertness, O.K.N. and F.I.N. are reliably elicited responses which, after a variable build up period, are maintained during the entire duration of the stimulus (Fig. 1). Apparently there is no habituation for these phenomena as opposed to the well known decrease of vestibularly-induced nystagmus over time (Crampton, 1964). In fact, the characteristics of O.K.N. and F.I.N. remain the same over prolonged periods of stimulation and after repeated daily sessions utilizing the same stimulus parameters. After cessation of the stimulus, both responses persist for a variable time depending upon the quality of the nystagmus during stimulation (Krieger & Bender, 1956; Pasik et al., 1970). These optokinetic afternystagmus (O.K.A.N.) and flicker-induced afternystagmus (F.I.A.N.) occur in the same direction of the preceding responses and show a progressive decrease in the frequency (Fig. 1). Eventually they are replaced by either random movements or a period of nystagmus in the opposite direction, i.e. an after-after response. O.K.A.N. and F.I.A.N. appear only if the cessation of the stimulus coincides with total darkness, and are immediately interrupted by illuminating the testing chamber. It should be emphasized that the after-after response, i.e. the inversion of the direction of nystagmus, is much more prominent in F.I.N. than in O.K.N.

Stimulus-response relationships have been studied for both phenomena (Pasik et al., 1970; Valciukas et al., 1973). The influence of stimulus temporal frequency (F_s), and therefore its effect upon nystagmus frequency (F) is of a similar nature in O.K.N. and F.I.N. The general function describing this relationship is of the

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A COMPARISON BETWEEN TWO TYPES OF VISUALLY EVOKED NYSTAGMUS IN THE MONKEY[1]

Pedro Pasik and Tauba Pasik

From the Department of Neurology Mount Sinai School of Medicine of The City University of New York N Y USA

Abstract Similarities between optokinetic nystagmus (O K N) and flicker-induced nystagmus (F I N) include response buildup and occurrence during the entire period of stimulation absence of habituation after nystagmus in the same direction occasional after-after nystagmus to the opposite side frequency spectrum, peak frequency and existence of lower and upper frequency thresholds. Phenomena are different in that for O K N the stimulus is in motion binocular and monocular stimulation are effective direction is determined by direction of motion unidirectionality is absent there is minimal influence of background illumination posture, labyrinthine receptors, and section of crossed optic fibers. For F I N the stimulus is stationary the response is elicited only by monocular stimulation the direction is determined by the stimulated eye there is exclusive unidirectionality it is abolished by background illumination, optic chiasm section and bilateral labyrinthectomy it is strongly influenced by posture. This comparison suggests that O K N and F I N are separate responses and that the effective stimulus for F I N may activate selectively the crossed optic fibers.

It has long been known that nystagmus of the eyes can be elicited by visual stimuli Traditionally this oculomotor response has been termed optokinetic nystagmus (O K N) since the proper stimulus is the motion of the optic targets. The quick phase is in the direction opposite to the stimulus movement This was the only known type of optically evoked nystagmus until 1965 when Costin Chaimovitz and Bergmann described a new kind of nystagmus elicited in the rabbit by stationary repetitive flashes of light (flicker) delivered to one eye In this case the quick phase was toward the side of the stimulated eye The observations were extended by Pasik et al (1970) who reproduced the phenomenon in the monkey A similar effect has since been observed in the cat (unpublished observations), but apparently cannot be obtained in man (Keane 1972) To date there is no clear explanation for flicker induced nystagmus (F I N) Several possible mechanisms have been offered recently (Pasik et al 1973) One possibility is that flicker stimulation evokes the perception of apparent motion which in turn could elicit an oculomotor response of a similar nature to O K N In view of this contingency it was considered useful to compare the two phenomena, O K N and F I N both in their absolute characteristics, and in the effects of manipulating the stimulus parameters, the posture of the experimental animal as well as the influence of the relative integrity of the visual and vestibular systems These are the purposes of the present communication

MATERIAL AND METHODS

The comparison is based on the results of previous studies on O K N and F I N (Pasik et al 1970 Valciukas et al., 1973 Valciukas, 1972 Pasik et al., 1973 T Pasik & P Pasik 1964 1972) to which certain preliminary new data have been added In total 48 monkeys (*Macaca mulatta*) were examined and tested either in the normal state or after interference with pregeniculate visual pathways and/or destruction of the

[1] We acknowledge with thanks the participation of Dr José A Valciukas in most of the original studies on which this report is based. The work was supported in part by N I M H Grant no MH-0-261 of the U.S. Public Health Service.

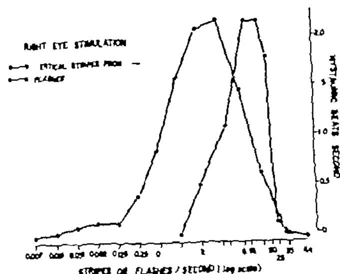


Fig. 4. Frequency spectra of O.K.N. and F.I.N. in normal monkey. Both curves derive from data of the same animal. Note the similarity of the positive acceleration portions which are practically parallel and show a linear increase of response frequency with the logarithm of stimulus temporal frequency. Peak responses are the same. The decline portions are somewhat different in this case. However group data showed better agreement (Pasik et al., 1970; Valciukas et al., 1973).

upper limit above which the response ceases to occur. According to the available data the upper threshold would be between 20 and 25 Hz at the tested luminance level.

Differences between O.K.N. and F.I.N.

The features on which O.K.N. anl F.I.N. differ are listed in Table II. A first consideration should be given to the characteristics of the stimuli which elicit one and the other type of nystagmus. It is clear that O.K.N. is evoked by successive moving stimuli traversing the visual field. Although there is a tendency to equate the slow phase of nystagmus with smooth pursuit eye movements and the fast phase with the saccades, it appears that the nystagmic beat is a unit which

Table II. *Differences between O.K.N. and F.I.N.*

Characteristics	O.K.N.	F.I.N.
1. Stimulus	In motion	Stationary
2. Binocular or monocular stimulation	Both	Monocular only
3. Determinants of direction	Direction of motion	Stimulated eye
4. Unidirectionality	Absent	Present
5. Effect of optic chiasm section	None	Abolition
6. Background illumination	Minor influence	Suppression
7. Influence of posture	Minor (?)	Major
8. Effect of bilateral labyrinthectomy	Minor	Abolition

is difficult to uncouple. In fact, lesions of the central nervous system affecting conjugate gaze in a particular direction interfere with all kinds of eye movements in that direction, namely smooth pursuit, saccades and optokinetic nystagmus as named by the direction of the quick phase (Bender 1969). The stimulus for F.I.N. is a flickering light which is stationary. There is no physical component of real motion in it, and a question that comes up is whether this kind of stimulus may be eliciting the perception of apparent motion, either through hallucinatory experiences characteristic of "stroboscopic patterns" (Smythies, 1959), or through a type of phi-phenomenon evoked by initial random saccades which would place the stationary source of light at successive spots on the retina (Pasik et al., 1970). Further experiments are needed to test this hypothesis.

Another major difference between O K.N. and F.I.N. is that the former may be obtained by stimulation of both eyes simultaneously or of each eye at a time. Contrariwise, F.I.N. can only be elicited under monocular stimulation conditions (Costin et al., 1965; Pasik et al., 1970), except on rare occasions when binocular stimulation has been observed to evoke a response of different characteristics (see below). The determinants of the direction of nystagmus, traditionally named by the quick phase, is also

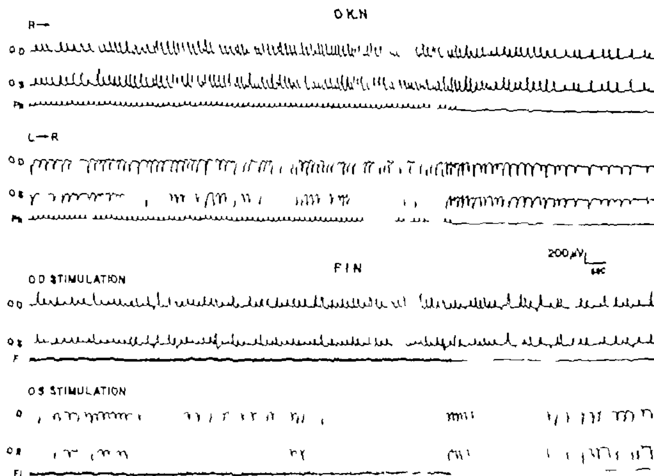


Fig. 1. Electro-oculograms of O.K.N., O.K.A.N., F.I.N. and F.I.A.N. in normal monkey. *R→L* and *L→R* indicate movement of optokinetic stimuli from right to left, and left to right respectively. *O.D.* right eye. *O.S.*, left eye. *Ph.*, photocell monitoring (2 Hz). *Fl.*, flicker monitoring (10 Hz). Note the initial build up of both responses, the similar peak frequencies, the occurrence of after nystagmus after cessation of stimulation, and its progressive decrease.

type $F = F(a + b \log F)$. Fig. 2 depicts the findings. It is clear that in both cases nystagmus frequency increases linearly with the logarithm of stimulus frequency to a peak and declines thereafter. The shift of the curves along the abscissa could well be due to the differences in the luminance of the stimuli, a factor which has been shown to modify the frequency spectrum of O.K.N. by its influence on the constant *a* (Valciukas et al. 1973). Comparable studies of the effect of luminance on F.I.N. are not available. It is interesting to note that the mean peak frequency of both O.K.N. and F.I.N., at least at the stimulus values chosen, are also similar and of the order of 2.0–2.5 nystagmic beats/second. These peak responses are elicited by stimulus temporal frequencies of about 4 Hz for O.K.N. and 10–15 Hz for F.I.N. This difference may again reflect the different luminance levels used. The tails of both curves presumably represent the regions where lower and upper thresholds are expected. Again there is a difference in the stimulus values eliciting lower threshold responses, which are of the order of 0.2 Hz for O.K.N. (Valciukas, 1973) and 2 Hz for F.I.N. (Pasik et al. 1970). The frequency of the response at threshold, however, is similar for both phenomena and of the order of 0.3 nystagmic beats/sec. The upper frequency thresholds have been shown to be strongly influenced by the luminance level in O.K.N. (Valciukas, 1972). Although no comparison can be made since these determinations are lacking for F.I.N., it is clear from the curves that F.I.N. has also an

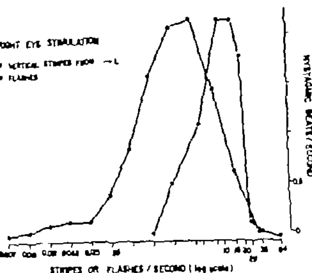


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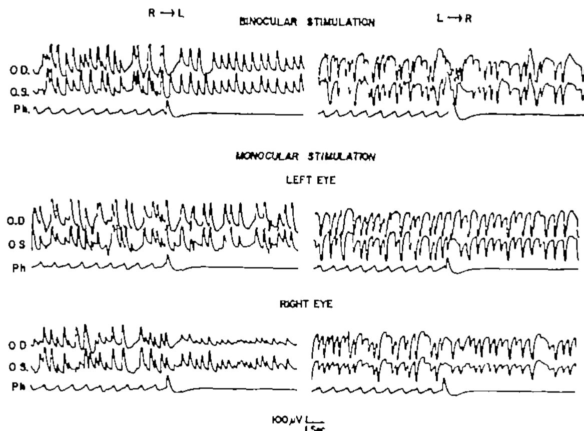


Fig 3 Electro-oculograms of O K.N and O K.A.N. under binocular and monocular stimulation in the normal monkey Notations as in Fig. 1 Note the similarity of responses and afterresponses under both testing conditions. Contrariwise, F I N is obtained only on monocular stimulation (see text).

different. In O K N it is given by the direction of the stimulus motion which is opposite to that of the response. The direction of F I N is determined by the stimulated eye the quick phase being to the right on stimulation of the right eye and to the left on stimulation of the left eye This is a constant feature of F.I N under any condition of testing. Although the quick phase may have an oblique component it has always a horizontal vector to the side of the stimulated eye. On the rare occasions when F I N was elicited also by binocular stimulation the nystagmus had a vertical character being usually upwards when the animal was tested in the erect position

Fukuda & Tokita (1957) were first to report the characteristic unidirectionality of O K N in lower *mammals* with almost totally crossed optic nerves, a finding previously noticed by other authors in birds (Huizinga & Meulen, 1951) It was found that rabbits and guinea pigs exhibited a similar O K N to the right and to the left under binocular stimulation whereas monocular stimulation evoked a *strong response* only when motion was toward the covered eye resulting in a nystagmus in the direction of the uncovered eye For example there was strong nystagmus to the right on stimulation of the right eye only when stripes moved from the right to the left. When the stripes moved from the left to the right the response was either absent or considerably weaker These authors pointed out that unidirectionality was not present in man and attributed this characteristic to the fact that approximately only 50 of the optic fibers cross at the optic chiasm in humans. Fig. 3 shows similar findings in the monkey which also carries about the same proportion of crossed/uncrossed fibers in the chiasm It can be seen that indeed there is no difference between O K N elicited under binocular or monocular conditions. On the other hand, F I N

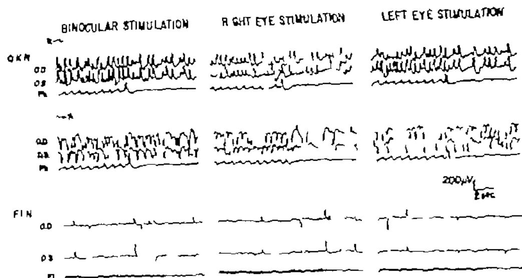


Fig. 4. Electro-oculograms from monkeys with midsagittal section of the optic chiasm during and after optokinetic or flicker stimulation. Notations as in Fig. 1. It is evident that severing all crossed optic fibers did not change the O.K.N. and O.K.A.N. even when elicited by monocular stimulation, whereas F.I.N. could not be obtained under any testing condition after the section.

shows a remarkable unidirectionality in the monkey. It can only be obtained to the right on stimulation of the right eye, and to the left on stimulation of the left eye. It should be recalled that F.I.N. was first discovered in the rabbit (Costin et al., 1965) and the question was raised whether the phenomenon could be due to the exclusive stimulation of one optic pathway since this animal has an almost total decussation of the optic nerves. It appears that the monkey reacts with respect to F.I.N. as if using only its crossed optic fibers.

The effect of midsagittal section of the optic chiasm in the monkey is relevant to this discussion. In fact, the discovery of unidirectionality of O.K.N. in lower mammals (Fukuda & Tokita, 1957) inspired us to attempt to reproduce it in reverse in the monkey by eliminating the crossed fibers. The hypothesis was that by creating a preparation with only uncrossed fibers, the unidirectionality of O.K.N. would become evident, but in the reverse direction to that shown by animals with totally crossed optic fibers. The results, originally reported in 1964 (T. Pasik & P. Pasik, 1964), are illustrated in Fig. 4, top. It is apparent that there was no difference between O.K.N. elicited under binocular and monocular conditions in monkeys with chiasm section. No unidirectionality was thus created. We further demonstrated that this was due to the fact that, although the crossed fibers were sectioned, the hemisphere ipsilateral to the stimulated eye made available visual information to the opposite hemisphere through the corpus callosum and perhaps through other brain commissures as well (Pasik & Pasik, 1972). Findings were dramatically different with respect to F.I.N. This phenomenon, which as shown above exhibits an exclusive unidirectionality with respect to the stimulated eye, was totally abolished by midsagittal section of the optic chiasm and did not recover for the entire 3 month follow up period (Fig. 4, bottom).

The influence of background light is considerably different for O.K.N. and F.I.N. The optokinetic response may be evoked in the presence of some levels of illumination provided there is enough contrast in the stimulus pattern. The flicker-induced response requires total darkness and it immediately ceases upon introduction of illumination in the testing chamber. Moreover F.I.N. is also abolished by stimulation of the

covered eye with a constant steady light (Costin et al. 1965).

It is well known that there is marked interaction between the visual and vestibular systems (Fukuda et al. 1957, Fukuda, 1959). Prompted by the latter studies, we attempted to investigate the influence of posture upon O.K.N. and F.I.N. Preliminary results on O.K.N. have shown no major differences in the response when elicited with the monkey in the erect position or in the right lateral or left lateral posture, using in every case stimuli moving to the right or to the left of the animal irrespective of its position. These results are apparently different than those obtained by Kurata (1958) who found such an influence present in birds. Although further studies are necessary to confirm our preliminary results, the data are still useful in terms of revealing a marked contrast with the influence of posture upon the direction and frequency of F.I.N. We have recently shown (Pasik et al. 1973) that the prevailing vector of F.I.N. has a component to the side of the stimulated eye in all positions tested, but there is also an oblique component which varies sinusoidally with the angle of tilt in the frontal plane (roll angle) and it is minimally influenced by tilts in the sagittal plane (pitch angle). Moreover, the direction of nystagmus at every tilt is strictly opposite when elicited by right or left eye stimulation. There are also changes in nystagmus frequency with tilts in the frontal plane which were similar for both eyes, being maximal in the upside-down and minimal in the lateral position. Since the influence of posture on F.I.N. could most possible reflect the function of the otolith organ, a first attempt was made to eliminate this influence by destruction of the labyrinths. The results were indeed unexpected: F.I.N. could not be elicited after bilateral labyrinthectomy in otherwise intact monkeys. It has been noted that although there are some O.K.N. changes in labyrinthectomized monkeys, the maximal effect is exerted on optokinetic afternystagmus (O.K.A.N.) which is permanently abolished by this lesion (Uemura & Cohen 1973). It appears therefore that the vestibular receptor organs are essential for F.I.N. and O.K.A.N. The meaning of this latter similarity is obscure.

COMMENTS

The preceding comparison revealed some similarities and major differences between O.K.N. and F.I.N. The similarities can be indicative of a common mode of reaction of the oculomotor system to repetitive visual stimuli whether they are in time and space (O.K.N.) or just in time (F.I.N.). The differences, however, suggest that the two responses are separate phenomena and consequently cast doubts on the interpretation that F.I.N. is merely a case of O.K.N. elicited by the perception of apparent motion. In earlier studies on oculomotor pathways we have shown that an adequate visual input must reach a given side of the brain to initiate an oculomotor output to the opposite side (P. Pasik & T. Pasik, 1964, T. Pasik & P. Pasik 1964). This conclusion applied to both conjugate gaze and O.K.N. Moreover, oculomotor output for vestibular nystagmus followed the same pattern. There is no reason to believe that F.I.N. behaves differently in this respect. Since F.I.N. is only elicited by monocular stimulation and occurs exclusively in the direction of the stimulated eye, it appears that the effective stimulus activates predominantly the phylogenetically older crossed optic fibers. This hypothesis is supported by the abolition of F.I.N. after chiasm section and by current findings in our laboratory showing that monkeys with one optic tract severed exhibit F.I.N. only when stimulation is delivered to the eye with preserved crossed fibers, i.e. the eye on the side of the lesion, and cannot be obtained from the other eye.

ZUSAMMENFASSUNG

Gleiche spezifische Eigenschaften zwischen optokinetischem Nystagmus (O.K.N.) und Nystagmus ausgelöst durch Flicker (F.I.N.), bestehen in gradueller Steigerung des Nystagmus und Fortbestehen während der ganzen Stimulierungsperiode; Abwesenheit von Gewöhnungseffekt; Nach-Nystagmus in die gleiche Richtung, dem gelegentlichen Auftreten von Nach-Nach-Nystagmus in die entgegengesetzte Richtung; dem gleichen Spektrum.

das beim der gleichen Hohenfrequenz und dem Bestehen von demselben *niedrigen und hohen* Frequenzgrenzen. Folgende Unterschiede bestehen für den O.k.N., der Stimulusgrenz ist von der Bewegung abhängig; binokulare und monokulare Stimulierungen sind wirksam, die Nystagmusrichtung wird durch die Richtung der Bewegung diktiert, Abwesenheit des einseitigen Nystagmus, dem Bestehen ... nur geringgradigem Einfluss von Hintergrundbeleuchtung, ... Position, Labyrinthrezeptoren und von dem Bereich der getrennten optischen ... Der Stimulus für den F.I.N. ist stationär, er wird nur durch monokulare Stimulierung ausgelöst; die Nystagmusrichtung wird durch die Stimulierung des Auges diktiert, dem Bestehen von ausschliesslich einer Nystagmusrichtung; er wird aufgehoben durch Hintergrundbeleuchtung, durch Durchtrennung des optischen ... und durch bilaterale Labyrinthektomie, und er ist stark von der Position des Stimulus beeinflusst. Diese Vergleichsuntersuchungen deuten an, dass der O.K.N. und der F.I.N. unterschiedliche neurologische Funktionen darstellen und dass der auslösende Stimulus für den F.I.N. vorwiegend auf dem Wege der gekreuzten optischen Fasern wirksam ist.

RÉSUMÉ

Les ressemblances entre le nystagmus optocinétique (O.K.N.) et le nystagmus induit par la scintillation (F.I.N.) sont: réponse en accroissement et occurrence pendant la période entière de stimulation, manque d'*habituation*, aprèsnystagmus dans la même direction; occasionnellement après-aprèsnystagmus vers le côté opposé; spectre de fréquence, *moment de fréquence et existence de seuils* de fréquence inférieur et supérieur. Les épiphénomènes sont différents parce que pour O.K.N. le stimulus est en mouvement; les stimulations monoculaires et binoculaires sont efficaces, la direction est déterminée par la direction du mouvement, l'unidirectionnalité est absente; l'influence de l'illumination de fond, de la posture, des récepteurs labyrinthiques et de la coupe du chiasma optique, sont mineures. Pour F.I.N., le stimulus est stationnaire, la réponse est provoquée seulement par la stimulation monoculaire; la direction est déterminée par l'oeil stimulé; l'unidirectionnalité est totale; la réponse disparait si le fond est illuminé, le chiasma est sectionné, ou s'il y a une labyrinthectomie bilatérale. La posture a une *forte influence. Cette comparaison suggère que l'O.K.N.* et la F.I.N. sont des réponses différentes et que le stimulus effectif pour le F.I.N. *peut activer avec prédominance* les fibres optiques croisées.

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G F Greiner C Conraux et M Collard

Strasbourg France

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Certes, le rôle du labyrinthe dans l équilibre est établi depuis les observations de Darwin en 1801 qui avait déjà noté l illusion de contre-rotation ressentie à l arrêt d un mouvement de rotation qu il effectuait autour de sa canne celles de Purkinje en 1820 de Flourens en 1824 de Ménière sur le plan clinique en 1861 Ce n est qu à la fin du siècle dernier que le nystagmus fût rattaché à une éventuelle lésion labyrinthique jusqu alors il était considéré comme un phénomène d origine oculaire (nystagmus des mineurs)

Si l essentiel de nos connaissances sur l appareil vestibulaire périphérique était donc acquis au début de ce siècle à la suite des études de Mach Bárány Buys, Hennebert, la notion de syndrome vestibulaire central ne s est progressivement individualisée qu à partir des travaux de neurologistes tels que Babinski André Thomas Van Gehuchten et surtout de Barre à partir de 1920 à Strasbourg Il eut le grand mérite d y consacrer la majeure partie de son activité et d élaborer une véritable séméiologie vestibulaire centrale. Ses élèves ont poursuivi son travail multipliant les observations cliniques, dégageant la symptomatologie vestibulaire de la symptomatologie cérébelleuse confrontant les données de la pathologie aux travaux anatomiques et physiologiques.

La mise au point depuis une quinzaine d années de l électronystagmographie clinique et de nouvelles techniques d examen et de stimulations physiologiques et non traumatisantes a abouti à l élaboration d une véritable vestibulométrie c est à dire à la possibilité de mesures précises des réponses vestibulaires à des stimulations connues, reproductibles et adaptées.

C'est à partir des documents d une telle confrontation otoneurologique que nous essayerons de cerner la notion de syndrome vestibulaire central et d en préciser les différents aspects.

I LE SYNDROME VESTIBULAIRE CENTRAL

A *La notion de syndrome vestibulaire central* s établit à partir des résultats de l expérimentation et des constatations cliniques.

En résumant très schématiquement les *données anatomiques et physiologiques* on peut dire que jusqu au niveau des noyaux vestibulaires primaires bulboprotubérantiels les expériences de stimulation et de destruction sont très comparables à celles faites sur le récepteur ou sur le nerf vestibulaire sitôt que l on s éloigne de ce niveau, les interférences deviennent extraordinairement complexes et le fonctionnement de l appareil vestibulaire se trouve intégré à trois systèmes différents bien que complémentaires

— l oculomotricité et ses connexions elle est le support du nystagmus,
— la motricité axiale et segmentaire u point de départ médullaire qui est l aboutissement du système vestibulo-spinal
— l activité psychique consciente à travers laquelle s exprime le trouble subjectif (ou vertige) qui peut résulter des lésions vestibulaires

C'est à dire que la perturbation de l'un ou de plusieurs de ces trois grands systèmes pourra *simuler* un élément du syndrome vestibulaire, mais pourra aussi *modifier l'expression* de celui-ci. Les exemples en sont nombreux en pratique

Ainsi l'existence d'un nystagmus spontané ne témoigne pas nécessairement d'une lésion vestibulaire d'autre part un nystagmus d'origine vestibulaire verra ses caractéristiques modifiées *dans le cas d'atteinte associée de* l'appareil oculo-*moteur* (parésie, ophtalmoplégie).

Ainsi également, certaines atteintes de l'équilibre axial sont sans rapport avec une lésion vestibulaire d'autre part, un syndrome vestibulo-spinal peut être difficile à caractériser en cas de troubles associés des cordons médullaires.

Ainsi enfin, il existe des troubles *qualifiés de vertiges* sans atteinte connue du système vestibulaire d'autre part, certains vertiges d'origine vestibulaire sont d'expression clinique très atypique du fait de lésions cérébrales ou de troubles psychiques.

Cela permet de comprendre que *la définition et les limites du syndrome vestibulaire central* sont extrêmement floues et difficiles à établir Une conception rigoureuse exigerait que, pour parler de syndrome vestibulaire il y ait à la fois des troubles subjectifs vertigineux, un syndrome clinique comportant nystagmus et déviations et des altérations des réponses vestibulaires instrumentales.

A l'inverse, une conception élargie va jusqu'à reconnaître le caractère vestibulaire à l'un quelconque de ces éléments, même isolé impression vertigineuse, ou nystagmus, ou déviations, ou anomalie de la réflectivité vestibulaire par exemple

Nous pensons que la notion et les limites des syndromes vestibulaires centraux ne peuvent être définis du point de vue anatomique, mais reposent sur une conception physiopathologique

A *l'état normal*, l'appareil vestibulaire fonctionne de manière purement inconsciente donc la prise de conscience d'une sensation de vertige témoignera soit d'une stimulation anormale, extraphysiologique (mal de mer par exemple), soit d'altérations propres à l'appareil vestibulaire. La notion de vertige nécessitera donc un examen clinique et des investigations vestibulométriques pour rechercher de telles altérations. L'absence de troubles subjectifs ne témoignera cependant pas d'absence de lésion vestibulaire et ne permettra donc jamais d'éliminer une atteinte de cet appareil.

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C'est donc par son intégration aux données du bilan vestibulométrique et de l'examen neurologique qu'un symptome clinique pourra être rattaché à une altération vestibulaire centrale.

B *Sémiologie clinique*

Elle est bien classique et sera simplement résumée.

Les troubles subjectifs sont faits de vertiges ou de sensations vertigineuses peu intenses, mal systématisées, mal définies par le sujet. Il faut mettre à part les grands vertiges rotatoires par lésion des noyaux vestibulaires primaires ceux *du syndrome de Wallenberg* et de certaines formes de sclérose en plaques, *qui rappellent* les vertiges du syndrome vestibulaire périphérique, probablement parce qu'ils sont effectivement dus à une lésion du premier neurone ou de la première jonction neuronale.

En dehors de ces cas, le vertige d'origine centrale *est fait le plus souvent d'*une impression de déséquilibre, d'une sensation d'insécurité, d'ébriété, volontiers déclenchée ou provoquée par certaines positions de la tête et du corps, de brève durée, peu gênante, mais contraignante par sa répétition pendant des semaines ou des mois. Ces troubles ne s'accompagnent pas souvent de *manifestations* végétatives sinon quelques rares nausées *et sont habituellement* améliorés par la fermeture des yeux. Ils *ne sont* en

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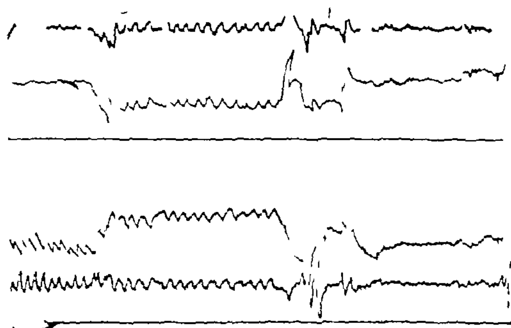


Fig 1 Nystagmus spontané de forme pendulaire d ori gine neurologique portant sur les 2 yeux dans le regard gauche (tracé du haut), dans le regard droit (tracé du bas).

général pas associés à des troubles auditifs latéralisés.

Les troubles subjectifs sont d autant plus importants que la lésion originelle s est installée brutalement que cette lésion est strictement unilatérale ou très asymétrique, que cette lésion est proche des noyaux vestibulaires primaires.

Les signes spontanés se manifestent en géné ral sous la forme d un syndrome vestibulaire dysharmonieux tel que l a défini Barré ou un syndrome parcellaire incomplet atypique

C *La séméiologie vestibulométrique* est d un apport souvent considérable pour le diagnostic topographique

S'il n existe que très rarement des signes pathognomoniques d une atteinte vestibulaire centrale certaines altérations cependant sont très évoca trices, et cette suspicion fait place à une quasi certitude lorsque plusieurs de ces signes sont retrouvés à l analyse du tracé nystagmographi que

L étude du regard

— la forme du nystagmus n est en général pas caractéristique à l exception du nystagmus rotatoire pur pratiquement toujours d ori gine bulbaire et du nystagmus pendulaire, d origine *neurologique ou oculaire* (Fig. 1 et 2)

— la nature du nystagmus. Un nystagmus multidirectionnel horizontal et vertical dans les différentes positions du regard est presque sûrement d origine neurologique (Fig. 3 et 4).

— la dissociation inter-oculaire du nystagmus. Un nystagmus spontané c est à dire dans le regard *direct* dissocié à prédominance monoculaire ou monoculaire pur (nystagmus ataxique de Harris) est toujours d origine centrale Il traduit une lésion de la bandelette longitudinale postérieure et se rencontre en particulier dans l ophtalmoplégie *internucléaire* Par contre la prédominance monoculaire légère sur l œil en abduction dans les regards externes n a que peu de valeur *localisatrice* (Fig. 5 et 6).

Les troubles de la réflectivité

— les altérations quantitatives. L *hyporéflectivité* unilatérale est essentiellement l apanage des

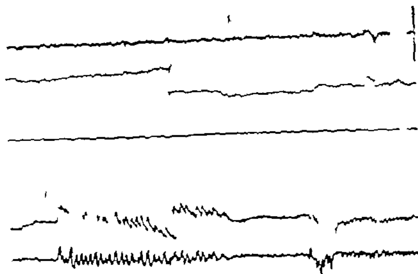


Fig. 2. Nystagmus spontané de forme pendulaire d'origine neurologique, vertical dans le regard vers le haut et vers le bas (tracé inférieur).

atteintes périphériques ou radiculaires. La compensation et le recrutement vestibulaires viennent en modifier plus ou moins les caractères sur le plan des réponses aux épreuves rotatoires, mettant ainsi en évidence les possibilités de régulation centrale dont ils permettent de tester le fonctionnement.

L'hyporéflectivité bilatérale a une signification plus ubiquitaire et peut s'observer aussi bien lors

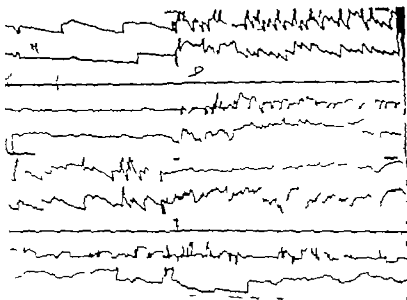


Fig. 3. Nystagmus spontané horizontal multiple dans les regards latéraux, à prédominance monoculaire, irrégulier dans un syndrome vestibulaire central (intoxication au Tegretol). Regard médian : rien; regard droit : nystagmus droit; regard gauche : nystagmus gauche.

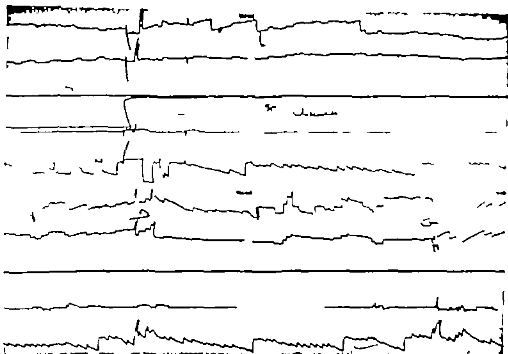


Fig 4 Nystagmus multidirectionnel, horizontal et vertical dans un cas de tumeur intra-protubérantielle. Regard médian nystagmus vertical supérieur regard droit nystagmus horizontal droit discret + nystagmus vertical supérieur regard gauche nystagmus oblique à gauche et en haut.

d une atteinte vestibulaire périphérique (ablotrophie intoxication) que lors d une atteinte centrale (*affections hérédodégénératives*, insuffisance circulatoire)

L hyper réflectivité surtout bilatérale est par contre volontiers le fait d une atteinte du système nerveux central Elle porte en général sur la réflectivité calorique et rotatoire et s accompagne

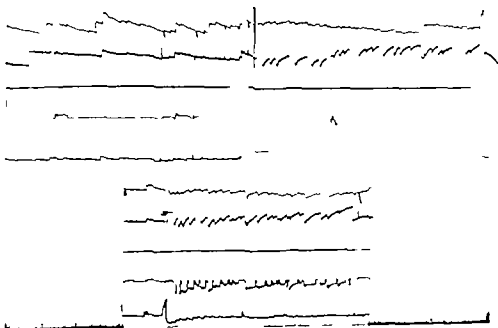


Fig 5 Dissociation inter-oculaire du nystagmus spontané dans un cas de sclerose en plaques. Regard droit discret nystagmus droit regard gauche idem au regard médian regard médian violent nystagmus gauche portant presque uniquement sur l'oeil gauche.

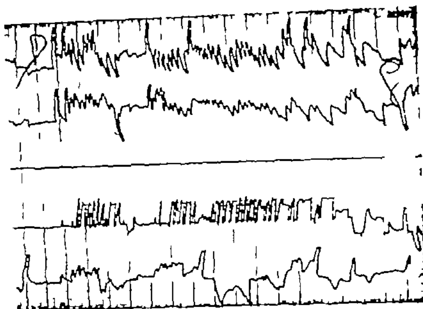


Fig. 6. Dislocation inter-oculaire du nystagmus spontané dans une ophtalmoplégie inter-nucléaire (intoxication aux hydantoïnes). Violent nystagmus horizontal droit dans le regard droit, portant essentiellement sur l'œil droit (tracé du haut) beaucoup moins sur l'œil gauche (deuxième tracé).

d'un nystagmus multidirectionnel du regard. La sclérose en plaque en est l'exemple le plus typique.

— les *altérations temporelles de la réflectivité* sont très typiques d'une atteinte centrale, fonctionnelle ou organique. L'épreuve rotatoire pendulaire qui interroge la réflectivité vestibulaire dans le temps, les fait bien apparaître.

Il en est ainsi de l'adaptation per-stimulatoire (ou tracé abrupt ou relapse vestibulaire), de l'habituation vestibulaire mise en évidence par les stimulations répétées.

— la *prépondérance directionnelle du nystagmus* est également un élément intéressant de localisation lorsqu'elle est étudiée à la fois sur la réflectivité calorique et rotatoire.

Un travail statistique personnel nous a permis de tirer les conclusions suivantes : si la prépondérance directionnelle n'existe *qu'à l'épreuve* calorique et n'est pas retrouvée à l'épreuve pendulaire, l'origine centrale est pratiquement certaine ; si la prépondérance à l'épreuve calorique est retrouvée à l'épreuve pendulaire, l'atteinte est presque toujours périphérique, surtout s'il existe en outre un nystagmus spontané.

— les *troubles du rythme nystagmique. Ils sont* plus ou moins marqués, allant de simples salves et inhibitions intermittentes des tracés éréthiques, peu significatives, aux tracés de « petite écriture » évocateurs de l'atteinte vasculaire de l'insuffisance vertébro-basilaire, et aux tracés désarticulés ou dysmétriques (Fig. 7, 8 et 9).

Ces dysrythmies, lorsqu'elles sont nettes et permanentes, portant d'ailleurs tant sur le nystagmus spontané que sur le nystagmus provoqué par les épreuves instrumentales traduisent une *atteinte centrale*, essentiellement en rapport semble-t-il avec un altération de la réticulée pontomésencéphalique.

— Le nystagmus de position est très *fréquemment* rencontré dans les atteintes vestibulaires centrales au niveau sus-tentoriel ou au niveau de la *fosse postérieure* : affections tumorales, traumatiques, vasculaires.

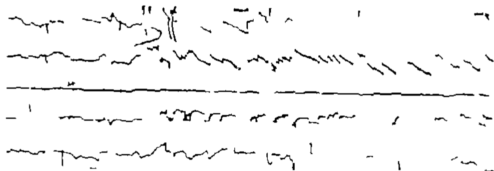


Fig 7 Troubles du rythme nystagmique. Nystagmus spontané horizontal droit dans une maladie de Friedreich.

Il n y a certes pas de nystagmus de position pathognomonique d une lésion centrale mais les caractères suivants en sont évocateurs nystagmus de type II de Nylén de direction constante apparaissant dans une ou plusieurs positions, inépuisable, reproductible nystagmus vertical inférieur en position de Rose discrétion ou absence habituelle des signes d accompagnement vertigineux ou végétatifs.

Ces caractères s opposent à ceux du nystagmus de position « périphérique » volontiers du type I de sens variable avec la position paroxystique s accompagnant souvent de troubles subjectifs vertigineux

— Le nystagmus d origine cervicale recherché par une épreuve simple permet d attirer l attention sur la pathologie du cou traumatique, vasculaire ou arthrosique

— L étude du nystagmus optocinétique bien qu il s agisse d une manifestation non vestibulaire est susceptible enfin de fournir des renseignements intéressants, d une part grâce à l étude des résultats de l interférence de la réaction optocinétique et du nystagmus spontané d autre part, grâce à la valeur topographique propre des anomalies optocinétiques.

Au cours des lésions hémisphériques l asymétrie optocinétique relève essentiellement d'une atteinte du lobe pariétal.

Au cours des lésions du tronc cérébral les perturbations du nystagmus optocinétique traduisent toujours une atteinte des voies oculogyres elles ont la valeur d une paralysie de fonction de niveau protubérantiel pour l altération du nystagmus horizontal, de niveau pédonculaire pour l altération du nystagmus vertical

Signalons enfin l intérêt de l inversion du nystagmus optocinétique dans l étude des nystagmus congénitaux

II ETUDE TOPOGRAPHIQUE ET ETIOLOGIQUE DES SYNDROMES VESTIBULAIRES CENTRAUX

A *Les atteintes du tronc cérébral*

Dans un tableau neurologique la constatation d un nystagmus et d autres signes vestibulaires oriente d abord vers une lésion du tronc céré

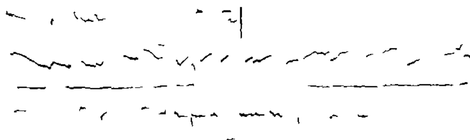


Fig 8 Troubles du rythme nystagmique. Nystagmus horizontal gauche dans une maladie de Friedreich. Regard droit nystagmus droit, regard gauche nystagmus gauche. *Désarticulation du tracé à la f*

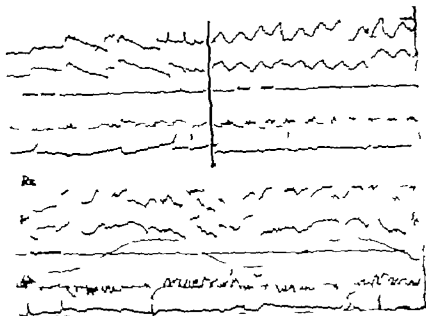


Fig. 9. La dysrythmie nystagmique se retrouve tant au niveau du nystagmus spontané, qu'au niveau de l'épreuve du mouvement de poursuite (pendule); qu'au niveau du nystagmus provoqué par l'épreuve rotatoire pendulaire. *Syndrome hérédo-dégénératif.*

bral c'est à dire leur fréquence et leur importance.

Toutes les affections traumatiques, dégénératives, tumorales, vasculaires, inflammatoires, lorsqu'elles touchent *le tronc cérébral* peuvent s'*accompagner* de signes vestibulaires, particulièrement d'un nystagmus.

Dans les *atteintes bulbaires*, la constatation d'un nystagmus rotatoire pur est classique et est dans les atteintes de cette région que l'on signale le plus fréquemment la possibilité de grands vertiges giratoires « ménièriformes », et qu'il est possible de noter des déviations nettes aux manœuvres, cependant habituellement dysharmonieuses.

Le nystagmus rotatoire pur est très fréquent au cours de la syringobulbie, seule lésion anatomiquement précise d'atteinte bulbaire. Il est homolatéral ou croisé par rapport à la lésion suivant le stade évolutif respectivement irritatif puis déficitaire. Ce nystagmus résume presque entièrement les données vestibulaires. La réflectivité en effet est peu altérée. Il n'y a pas de vertiges.

Le syndrome vasculaire latéro-bulbaire (Wallenberg) est une éventualité beaucoup plus fréquente. Il est souvent inauguré par un grand vertige rotatoire. Le nystagmus spontané peut être giratoire pur, mais aussi horizontal battant en général du côté opposé à la lésion, traduisant alors probablement une lésion plus diffuse. Les épreuves instrumentales montrent une hyporéflectivité uni- ou bilatérale et le plus souvent une dysrythmie nystagmique.

Dans les atteintes bulbo-protubérantielles ou protubérantielles, le syndrome vestibulaire n'est pas aussi schématique que dans les lésions bulbaires pures. Anatomiquement, il peut exister des lésions de l'ensemble des noyaux vestibulaires primaires, mais les connexions cérébello-vestibulaires et vestibulo-oculogyres expliquent que dans la plupart des cas, il existe une association de facteurs.

Sur le plan étiologique, cette région est essentiellement atteinte soit par des lésions vasculaires d'origine basilaire, soit par des tumeurs (du tronc, du 4e ventricule ou des annexes venant comprimer le tronc), soit dans la sclérose en plaques. Dans l'un ou l'autre de ces cas, les lésions sont habituellement assez diffuses et difficiles à systé-

matiser Le nystagmus horizontal ou multidirectionnel est le plus souvent rencontré.

Dans les cas de tumeurs, la composante verticale est fréquente pour les localisations médianes la composante horizontale pour les localisations latérales.

La réflectivité aux épreuves est modifiée de façon variable mais deux altérations sont souvent rencontrées la prépondérance directionnelle du nystagmus qui répond à la description de la dysréflexie oculovestibulaire croisée de Barre, pouvant aboutir à l'hémi avestibulie, et les troubles du rythme nystagmique avec désorganisation du pattern au niveau du tracé comme au niveau « élémentaire » de la secousse, traduisant l atteinte de la réticulée mésencéphalique et de la bandelette longitudinale postérieure Il s agit là d ailleurs de lésions du versant oculogyre du réflexe vestibulo-oculogyre, dont la spécificité vestibulaire peut être discutée

Dans les atteintes pédonculaires Le nystagmus spontané vertical pur est classique (tumeurs de la calotte, syndrome alterne de Weber encé phalopathie de Gayet Wernicke) Il est volontiers dissocié, plus rarement un nystagmus rétrac torius, extravestibulaire peut se manifester

Ce type de nystagmus vertical apparait essentiellement comme une perturbation de la motricité oculaire conjuguée verticale et son origine vestibulaire est plus que discutable (véritable « pace maker » anormal sur les voies de la verticalité)

Le nystagmus vertical s associe d ailleurs très souvent aux paralysies de la verticalité et aux altérations du nystagmus optocinétique vertical. Il n existe habituellement pas de perturbations aux épreuves vestibulaires, mais leur interprétation peut être délicate du fait de signes oculomoteurs spontanés et aussi de la fréquente interruption « fonctionnelle » des liaisons vestibulo-oculomotrices, et on peut faussement conclure dans ces cas à *une aréflexie* vestibulaire du fait de l'absence de réponse nystagmique aux stimulations caloriques ou rotatoires.

B *Dans les affections du cervelet* essentiellement d origine tumorale dégénérative quelquefois infectieuse (abcès du cervelet) il existe très fréquemment un nystagmus horizontal multiple ou vertical.

— il peut être *spécifiquement cérébelleux* nystagmus des regards latéraux, souvent pendulaire, tremblement du regard « nystagmus postural » d Alajouanine et Lhermitte
— il s agit le plus souvent d un nystagmus « vestibulaire des cérébelleux » le trouble de la *fonction cérébelleuse* modifiant les caractères du nystagmus vestibulaire nystagmus spontané multiple irrégulier dysmétrique visqueux, crocheté tous ces caractères sont retrouvés également pour le nystagmus provoqué par les épreuves caloriques et rotatoires.
— *le* nystagmus de position est très fréquent dans les atteintes cérébelleuses.

C. *Dans les atteintes de la base* (Parkinson, encéphalites), le nystagmus spontané est rare mais on rencontre par contre souvent des perturbations de l oculomotricité désordre des mouvements oculaires volontaires, successions de saccades, altérations du mouvement de poursuite

D *Au cours des atteintes hemispheriques* les troubles vestibulaires sont contingents nystagmus spontané rare épreuves instrumentales *habituellement normales, mis à part* la possibilité d une prépondérance directionnelle du nystagmus, retrouvée d ailleurs également à *l'épreuve optocinétique ce qui fait mettre* en doute son caractère vestibulaire spécifique Le nystagmus de position est quelquefois rencontré.

Contrastant avec la discrétion des troubles vestibulaires, les troubles de l équilibration dont l origine est d ailleurs fort complexe sont fréquents.

Ces constatations semblent bien confirmer les données physiopathologiques concluant actuellement à l absence de projections vestibulaires corticales spécifiques.

CONCLUSION

Il faut souligner les difficultés de la définition et des limites des syndromes vestibulaires cen

traux. Il convient surtout de replacer le rôle de l'appareil vestibulaire dans le grand mécanisme de *l'équilibration.*

Sur le plan physiopathologique, il semble préférable de proposer une division de l'appareil vestibulaire en deux niveaux, qu'il n'appartient plus de qualifier formellement de « périphérique » ou de « central »

Un niveau de réception et de transmission qui comprend, outre le récepteur labyrinthique et le nerf vestibulaire, les noyaux vestibulaires primaires ou tout au moins la jonction interneuronale. Son atteinte est responsable de vertiges systématisés (dans les *lésions* aigues), de nystagmus intense, habituellement régulier et unisens, de déviations, d'altérations harmonieuses aux épreuves. Au cours des maladies du système nerveux central, il est rencontré surtout dans les syndromes vasculaires (insuffisance vertébrobasilaire permanente, Wallenberg), et certaines formes de sclérose en plaques.

Un niveau d'intégration qui comprend les liaisons des noyaux vestibulaires primaires au système oculo-moteur au cervelet, à la moelle principalement, mais aussi à l'ensemble de l'appareil d'équilibration y compris ses afférences conscientes.

Les lésions du système nerveux central qui touchent cet étage ne seront donc jamais univoques, et s'il y a atteinte prédominante des structures vestibulaires centrales, les signes seront habituellement parcellaires, variables et surtout *associés ou combinés.*

Toutes les atteintes du système nerveux, mais particulièrement celles du tronc cérébral pourront en être responsables, qu'elles soient vasculaires, traumatiques, inflammatoires, tumorales, dégénératives.

La spécificité vestibulaire de leurs manifestations cliniques ou instrumentales peut cependant souvent prêter à discussion et il reste toujours nécessaire de les intégrer à l'ensemble de l'étude du système nerveux.

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DIE REAKTION DER MITTELOHRSCHLEIMHAUT BEI TUBENVERSCHLUSS[1]

W Arnold und K H Vosteen

Aus der Hals-Nasen-Ohrenklinik der Universität Frankfurt/M., Bundesrepublik Deutschland

Abstrakt 1 Ein Verschluß der Ohrtrompete bewirkt durch den sehr rasch einsetzenden Unterdruck in der Pauke nach wenigen Stunden eine erheblich vermehrte Passage von Extrazellularflüssigkeit durch das Schleimhautepithel hindurch in das Lumen der Paukenhöhle. Nach 24 Stunden kommt es zur Ruptur der Interzellularbrücken und die Flüssigkeit des subepithelialen Raumes ergießt sich frei in die Pauke.

2 Bei anhaltendem Unterdruck in den Mittelohrräumen beobachtet man eine zelluläre Umdifferenzierung der vormals flachen Epithelzellen zu hochprismatischen Epithelzellen mit neuartiger Funktion Das einschichtig flache Epithel wird beinahe vollständig durch zylindrische kinozilientragende oder sekretorisch aktive Zellen ersetzt.

3 *Frühzeitige Belüftung des „Hydrops ex vacuo"* führt zu einem Sistieren der epithelialen Umwandlung, jedoch nicht zu einer Rückbildung auf den ursprünglichen epithelialen Zustand

4 Untersuchungen an menschlichen Schleimhautproben des Mittelohres zeigen, daß die Schleimhautveränderungen bei seröser Otitis den gleichen Gesetzen unterworfen sind, wie sie sich im Tierexperiment reproduzieren lassen.

Ohrtrompete und Mittelohrräume bilden sowohl anatomisch als auch funktionell eine Einheit (Link & Handl, 1954 Handl & Link, 1954 Feldmann 1973*a*, *b*) So führen stenosierende Veränderungen im Bereich des Tubenverlaufes zwangsläufig zu pathophysiologischen Auswirkungen auf die lufthaltigen Räume des Mittelohres, deren morphologisches Substrat sich in einer Veränderung des epithelialen Gefüges der Mittelohrschleimhaut niederschlägt Wie wir anhand von Trazerstudien im Tierexperiment zeigen konnten (Arnold 1971) besteht zwischen Liquor cerebrospinalis, der Perilymphflüssigkeit des Innenohres und der Extrazellularflüssigkeit des subepithelialen Raumes der Mittelohrschleimhaut eine offene Kommunikation. Zude wurde der Nachweis erbracht daß Flüssigk aus dem Interstitium des subepithelialen Raum auf cytopemptischem Wege ständig an d Oberfläche des Schleimhautepithels transportie wird. Die umgekehrte Richtung, nämlich e cytopemptischer Transport von der Oberfläch des Mittelohrschleimhautepithels in den sub mukösen Raum hinein scheint nach Untersu chungen von Hölt (1969) nicht möglich zu sein Somit konnte nachgewiesen werden, daß d normale Mittelohrschleimhaut nur in eine Richtung, nämlich vom subepithelialen Raun zur Paukenhöhle Flüssigkeit transportiert. Al Ergebnis einer anschließenden Untersuchun (Arnold, 1972) konnten wir feststellen, daß e nach Provokation eines Paukenergusses durch Verkauterung des Tubenostimus zuerst zu einem *vermehrten transepithelialen cytopemptischen* Transport von Extrazellularflüssigkeit an die Oberfläche der Mittelohrschleimhaut kommt und wenige Stunden später der zunehmende hydrostatische Druck im subepithelialen Raume eine Ruptur der epithelialen Schlußleisten bewirkt Zu diesem Zeitpunkt kann subepitheliale Extrazellularflüssigkeit ohne zelluläre Barriere frei in das Lumen der Paukenhöhle übertreten wobei man elektronenmikroskopisch nachweisen kann daß nun auch in zunehmendem Maße ein *Gefäßtranssudat bei der Produktion* der Flüssigkeit beteiligt ist Gleichzeitig beobachteten wir eine sehr rasch eintretende Umwandlung des epithelialen Bildes Ortsständige *flache* Epithelzellen wurden durch hochprismatische schleimproduzierende Zellen ersetzt Diese be

[1] Herrn Prof Dr Tadashi Fukuda, University School of Medicine, Gifu, Japan in Verehrung gewidmet.

rens vielfach beschriebene epitheliale Metaplasie (Holmgren, 1940; Sadé et al., 1959; Senturia et al., 1961; Senturia et al., 1962; Senturia, 1963; ...71; Friedmann, 1963; Sadé, 1966; Reiner & ...ner, 1969; Paparella et al., 1970; Proud et al., ...70; Arnold, 1972) muß zu einer neuartigen ...nktion der Epithelzellen führen.

Zweck der vorliegenden tierexperimentellen und vergleichenden Untersuchung soll es sein aufzuzeigen, *bis zu welchem Zeitpunkt* Veränderungen an der *Mittelohrschleimhaut* bei stenosierender Ohrtrompete durch bald einsetzende Belüftungsmaßnahmen reversibel sind und von welchem morphologischen Zustandsbild ab die metaplastisch umgewandelte Mittelohrschleimhaut eine nicht mehr zu beeinflussende selbständige Funktion übernommen hat.

Voraussetzung für derartige *Untersuchungen* ist eine genaue Kenntnis der normalen epithelialen Verhältnisse beim angewandten Laboratoriumstier und beim Menschen. Lim et al. (1967) untersuchten elektronenmikroskopisch die Auskleidung der Eustachischen Röhre und die Region des tympanalen Tubenostiums beim Meerschweinchen. Hier fanden sie schleimproduzierendes Epithel durchsetzt von Becherzellen und Zellen mit dunklen Schleimblasen, die insbesondere in der Übergangszone zwischen tympanalem Tubenostium und Hypotympanon zu finden waren. Hussl & Lim (1969), Hentzer (1970) und Lim et al. (1973) beschrieben die Ultrastruktur der Mittelohrschleimhaut des Menschen anhand von Autopsiematerial, wobei *sie sich fast ausschließlich dem tubenauskleidenden Epithel und der Übergangszone* zwischen tympanalem Tubenostium und Hypotympanon zuwandten. Sie konnten zeigen, daß insbesondere in der Übergangszone von Tube zu Hypotympanon zilientragende Zellen vorkommen, gelegentlich auch vereinzelte Schleimzellen. Andere Veröffentlichungen, denen zufolge der Schleimhaut des Mittelohres grundsätzlich *in allen* topographischen Bereichen sekretorische Funktion zugesprochen wird, können nur mit vorsichtiger Kritik aufgenommen werden (Bak-Pedersen & Tos, 1971a, b), nicht nur weil das Material von Toten entnommen wurde, deren Anamnese nicht bekannt war, sondern weil mehrfach belegt wurde, daß jede länger anhaltende Tubenfunktionsstörung zu einer epithelialen Umwandlung der Mittelohrschleimhaut führt (Friedmann, 1955; Senturia et al., 1962; Zechner et al., 1968; *Lim & Birck, 1971; v. Ilberg & Arnold, 1972; Arnold & v. Ilberg, 1973; Arnold, 1972*). Wenn Sadé (1966) die menschliche Mittelohrschleimhaut gleichsetzt mit „respiratorischem Epithel", so trifft das sicherlich für die unbelastete gesunde menschliche Mittelohrschleimhaut nicht zu. Auch eine entzündungsfreie Mittelohrschleimhaut nach Tympanoplastik ist keinesfalls wie Schöndorf (1974) vermutet, identisch mit gesunder, nicht vorbelasteter Schleimhaut. Das mehrschichtigem zilientragende und sekretorisch potente Epithel ist ebenso wie die starke Fibrosierung der Submucosa ein Hinweis für den vorangegangenen entzündlichen Prozeß. Hier liegt eine echte metaplastische Umwandlung vor, auf die wir experimentell (Arnold, 1972) und vergleichend (Arnold & v. Ilberg, 1973) aufmerksam gemacht haben. Selbst Gewebeproben von der ovalen Fensternische, von der Fußplatte oder vom Promontorium — im Verlaufe einer Otosklerose-Operation gewonnen — dürfen keinesfalls für „normale" Mittelohrschleimhaut angesehen werden, wie es Schöndorf & Mäusle (1973) taten. Ihre vorgelegten Abbildungen weisen eindeutig jene Veränderungen auf, wie wir sie in einer ausgedehnten Untersuchungsreihe als kennzeichnend für Schleimhautveränderungen bei Otosklerose sahen (Arnold & Plester, *1974). Dagegen ließen zahlreiche* Biopsien von Mittelohrschleimhaut, welche bei Otosklerosekranken fern vom Otoskleroseherd entnommen wurden, in allen Fällen ein flaches bis kubisches Epithel erkennen, in das gelegentlich eine einzelne zilientragende Zelle eingestreut lag, das jedoch ohne Ausnahme keine schleimproduzierenden Zellen trug (vergl. Kawabata & Paparella, 1969; Paparella, 1973).

Grundsätzlich können wir davon ausgehen, daß die unbelastete, gesunde Mittelohrschleimhaut beim Meerschweinchen (Lim et al., 1967; Hayes, 1973; Hussl & Lim, 1969), wie auch die des Affen (Kawabata & Paparella, 1971) und

die des Menschen (Gosepath, 1964; Eckert-Möbius, 1926; Bargmann, 1962; Hussl & Lim, 1969) mit Ausnahme des Tubenwinkels ein flaches, zilienloses und schleimdrüsenloses Epithel aufweist. Veränderungen des epithelialen Gefüges im Tierexperiment und bei bestimmten Schleimhauterkrankungen des menschlichen Mittelohres werden wir nach diesen Ausgangskriterien interpretieren.

MATERIAL UND METHODE

I) Bei 24 Meerschweinchen wurde in Nembutalnarkose das epipharyngeale Tubenostium der rechten Seite mit einem Thermokauter verödet (Methodik, Arnold, 1972) und anschließend die Tiere nach 10, 16, 20, 24 und 48 Stunden sowie nach 3, 6, 8 und 14 Tagen durch korporale Perfusion mit 6,2 %igem Glutaraldehyd (Karlsson & Schultz, 1965) getötet. 30 Minuten vor der korporalen Perfusion wurde die Membrana atlanto-occipitalis freigelegt und 100 µl Thorotrast in die Cisterna cerebello-medullaris injiziert. Nach anschließender Immersionsfixation des entsprechenden rechten Felsenbeines wurden Schleimhautproben vom ovalen Fenster, vom Schleimhautüberzug der Cochlea und vom runden Fenster entnommen, in Phosphatpuffer ausgewaschen und mit Osmiumtetroxyd (1 %ig) nachfixiert, in Alkohol dehydriert und schließlich in Epon (Luft, 1961) eingebettet. Zur Kontrolle wurden von der linken Bulla tympanica ebenfalls die topographisch korrespondierenden Schleimhautstellen entnommen und zur Untersuchung miteingebettet.

II) Kreuzversuch: Um sicherzustellen, daß tatsächlich nur die durch den Tubenverschluß hervorgerufenen hydrostatischen Veränderungen für die Schleimhautmetaplasie verantwortlich sind, wurde in einer weiteren Untersuchungsreihe bei 9 Meerschweinchen unter gleichen experimentellen Bedingungen wie oben vorgegangen, allerdings wurde bei diesen Tieren nach 20 Stunden, 24 Stunden, 2 Tagen, 4 Tagen und 15 Tagen jeweils das rechte Trommelfell total entfernt, um den Einfluß einer Belüftung auf die weitere Reaktion der Mittelohrschleimhaut bei verschlossener Ohrtrompete zu studieren. Alle Tiere wurden bis zur Tötung antibiotisch mit Ambliosin (Hoechst) abgedeckt. Demzufolge konnten wir bei keinem Tier Zeichen einer bakteriellen Entzündung licht- wie auch elektronenmikroskopisch erkennen.

III) Bei 7 Patienten wurde während einer Stapesmobilisation wegen Otosklerose Schleimhaut fern vom otosklerotischen Herd entfernt (vorderer Anteil der runden Fensternische, Fazialiskanal, Promontorium) und zur vergleichenden Untersuchung elektronenmikroskopisch aufgearbeitet.

IV) Zum weiteren Vergleich wurden Schleimhautproben von 12 Patienten mit fadenziehendem oder wässrigem Paukenguß entnommen, bei denen entweder eine erweiterte Parazentese oder eine Paukenrevision vorgenommen worden war. Die Schleimhautproben wurden vom Promontorium, von der Gegend des runden Fensters oder vom Aditus ad antrum gelöst. Die Immersionsfixation und Weiterbehandlung dieser Gewebeproben erfolgte mit gleicher Methodik wie oben. Die elektronenmikroskopischen Dünnschnitte wurden mit Bleicitrat (Reynolds, 1963) und Uranylazetat (Huxley & Zubay, 1961) nachkontrastiert. Von allen eingebetteten Geweben wurden Schnitte zur histographischen Orientierung angefertigt und mit Paraphenyldiamin oder Azur 2 Mallory gefärbt.

BEFUNDE

I) Die normale, nicht vorbelastete Mittelohrschleimhaut des Meerschweinchens ist aus zwei Schichten aufgebaut. Sie besteht aus einer einschichtigen, flachen Epithellage, die an der Oberfläche nur vereinzelt kurze Mikrovilli trägt. Das Cytoplasma ist aufgelockert und beinhaltet in der Regel zahlreiche optisch leere pinozytotische Bläschen. Gegen das tympanale Tubenostium hin geht das flache Epithel in ein kubisches Epithel über, das an vielen Stellen nun zweireihig ist, bestehend aus einer basalen Zellage von kleinen runden Zellen und einer hochprismatischen zilientragenden Epithelschicht. Dazwischen sind schleimproduzierende

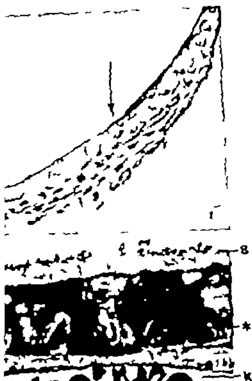


Abb. 1 ( ) Lichtmikroskopische Wiedergabe der histotopischen Verhältnisse im Tubenwinkel (Meerschweinchen) ↗ plötzlicher Übergang von flachem zu hochprismatischem Epithel. 450 (b) Undifferenziertes Epithel vom Schleimhautüberzug der Cochlea 3 Tage nach Verödung des gleichseitigen Tubenostiums. Über dem zweischichtigen zylindrischen Epithel liegt ein dünner Schleimfilm (SF); K, weitgestellte Kapillare; nach basal abgedrängte Epithelzelle (s. Abb. 3). 1250

Zellen eingestreut. Die Grenze von flachem Epithel zu hochprismatischem zweischichtigem Epithel ist beim Meerschweinchen plötzlich (Abb. 1). Die nach basal folgende submuköse Schleimhautschicht umfaßt den Bereich zwischen Epithel mit Basalmembran und knöcherner Unterlage. Dieser Raum wird von einem sehr lockeren, weitmaschigen fibrozytären Gewebe gestaltet, in dessen Maschen lockere Bündel von kollagenen und wenigen elastischen Fasern verlaufen. Die vereinzelt anzutreffenden, teilweise mit glatter Muskulatur ausgestatteten Gefäße liegen unterhalb der Basalmembran und können die Epithelschichten in das Lumen der Paukenhöhle vorwölben.

Gelegentlich trifft man Bündel von Nervenfasern in der submukösen Schicht, die von einer flachen Schwannschen Zellage umgeben sind und nur in seltenen Fällen eine Myelinisation zeigen. Diese Nervenbündel sind der Jacobsonschen Anastomose zuzuordnen. Gegen den angrenzenden Extrazellularraum sind die Axonenbündel mit einer dichten Basalmembran abgegrenzt. Eine besondere Stellung nimmt die Membran des runden Fenster ein, bei der es infolge fehlender knöcherner Wandstruktur der Cochlea zu einem freien Übertritt von perilymphatischer Flüssigkeit in die weiten Extrazellularräume der Submucosa kommt. Eine zelluläre Barriere zwischen Scala tympani und subepithelialem Raum besteht nicht. Hier verbindet sich das mesenchymale, locker geschichtete Endost der Cochlea mit dem Fibrozytenschwamm der Submucosa und gestattet den Flüssigkeiten freien Austausch.

II) Die Ergebnisse dieser Versuchsserie, bei der in bestimmten Zeitabständen nach Verödung der Tube Mittelohrschleimhaut untersucht wurde, stimmen mit früheren Befunden (Arnold, 1972) überein. 10 Stunden nach Verödung der Tube beim Meerschweinchen bemerkt man eine erhebliche Vermehrung der Pinocytosebläschen im Epithel als Ausdruck einer zunehmenden cytopemptischen Tätigkeit. Gleichzeitig kommt es zu einer Erweiterung des interzellulären Raumes zwischen den Epithelzellen. Nach 16 Stunden sieht man, daß die weit gestellten interzellulärräume mit Bündeln von kollagenen Fasern ausgefüllt sind. Schließlich kommt es zur Ruptur der Interzellularbrücken und die Flüssigkeit des subepithelialen Raumes strömt in die Paukenhöhle. Schon vorher kann man an vielen Epithelzellen die ersten Anzeichen einer zellulären Gegenreaktion feststellen. Das ursprünglich gleichförmig helle Grundcytoplasma nimmt an elektronendichter Substanz zu, wobei es zu einer Vermehrung von lysosomalen Strukturen und Mitochondrien kommt. Zellkerne zeigen tiefe Einschnürungen sowie eine Umorientierung ihrer Chromatinstruktur. Der gesamte Zelleib quillt auf. So entsteht aus der vormals langgezogenen, flachen Epithelzelle eine kubisch bis





Abb 2. (*a*) Normaler Schichtenaufbau der Mittelohrschleimhaut des Meerschweinchens (Paukenboden). *E*, Epithel, einschichtig und flach *Bm*, Basalmembran *F* Fibrocyt *Px*, Plexus tympanicus *L*, Lumen der Paukenhöhle *EZR*, weiter subepithelialer Extrazellularraum, * Cytopempsisbläschen. 10 000. (*b*) Schleimhautepithel om P kenboden 16 Stunden nach Tubenverschluß. mehrschichtiges Epithel, erweiterte Interzellularspalten fi gerförmige Interzellularbrücken *L*, Lumen der Paukenhöhle *Bm* Basalmembran *Th*, Cytopempsisbläschen mit Thorotrast gefüllt. 17 500.



Abb. 3 48 Stunden nach Tubenverschluß. Schematisches Bild mit elektronendichten Schleimblasen (M) und [illegible] stark erweiterte Interzellularräume um die nach basal verdrängten ursprünglichen Epithelzellen; L, Lumen der Paukenhöhle; Bm, Basalmembran. 7000.

hochprismatische Zelle, die zur benachbarten Epithelzelle hin pseudopodienartige Ausläufer entsendet. Zwischen diesen Ausläufern entwickeln sich primitive Schlußleisten im Sinne von Zonulae adhaerentes. Verschiedene Anzeichen, wie die erwähnte Chromatin-Umorientierung, die tiefen Kerneinbuchtungen, das Auftreten von Zentriolen im Grundcytoplasma und die vielerorts plötzlich vorhandene Mehrschichtigkeit des Epithels lassen Zellteilungsvorgänge vermuten (Abb. 2*a*, *b*).

Im apikalen Cytoplasmabereich der neuartigen hochprismatischen Epithelzellen liegen etwa einen Tag nach Verschluß der Ohrtrompete relativ elektronendichte, opake, kreisrunde Einschlüsse. Basal entsenden diese Zellen sehr lange, sich verzweigende Ausläufer, welche in die weit offenen, benachbarten Interzellularfugen hineinreichen und mit den ortsständigen Epithelzellen Interzellularbrücken ausbilden. An der basalen Fläche erkennt man die Neubildung von Basalmembranen.

Nach 48 Stunden lassen sich stark erweiterte und rupturierte Interzellularspalten mit Austritt von subepithelialer Flüssigkeit nurmehr im Bereich des runden Fensters nachweisen, wogegen sich in fast allen anderen Bereichen des Mittelohres ein neuartiges epitheliales Gefüge ausgebildet hat. In den basal noch weit offen stehenden Interzellularräumen liegen abgerundete, ursprüngliche Epithelzellen, die zum Teil noch mit großen, wassergefüllten Blasen in ihrem Cytoplasma ausgefüllt sind. Darunter hat sich eine kontinuierliche, an keiner Stelle unterbrochene Basalmembran formiert. An ihrer lumenwärts gerichteten Oberfläche zeigen die hoch-

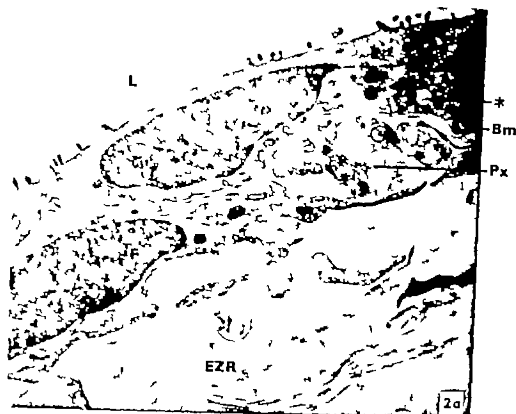




Abb. ( ) Normaler Schichtenaufba der Mittelohrschleimhaut des Meerschweinchens (Paukenboden). *E*, Epithel, einschichtig und flach. *Bm*, Basalmembran. *F*, Fibrocyt. *Px*, Plexus tympanicus. *L*, Lumen der Paukenhöhle. *EZR*, weiter subepithelialer Extrazellularraum. Cytopempsisbläschen. 10 000. (*b*) Schleimhautepithel vom Paukenboden 16 Stunden nach Tubenverschluß: mehrschichtiges Epithel, erweiterte Interzellularspalten, fingerförmige Interzellularbrücken. *L*, Lumen der Paukenhöhle. *Bm*, Basalmembran. *Th*, Cytopempsisbläschen mit Thorotrast gefüllt. 17 500



Abb. 5 14 Tage nach Tubenverschluß. Komplett undifferenziertes Epithel aus dem Bereich des Runden Fensters. L, Lumen der Paukenhöhle; Z, Zilientragende Epithelzellen; apokrine Sekretion. ×4 000.

er das runde Fenster in die weiten Extrazellu-
rräume der Mittelohrschleimhaut gelangt, nun
urch die starke Bindegewebsvermehrung zu-
ückgehalten wird und nunmehr in den weni-
en, vorzugsweise basal gelegenen Lymphspalten
achzuweisen ist (Abb. 4). Der rege cytopemp-
ische Flüssigkeitstransport aus dem submukö-
sen Raum durch das Epithel hindurch an die
Oberfläche der Schleimhaut läßt sich jetzt nicht
mehr nachweisen. Der Sekretionstyp der sekre-
torisch aktiven Epithelzellen läßt eine apo-
krine und ekkrine Sekretion unterscheiden (Abb.
5, 6).

III) Um zu entscheiden, ob diese Undifferen-
zierungsvorgänge des Epithels, welche zweifellos
auf das Vakuum in den Mittelohrräumen nach
Tubenverschluß zurückzuführen sind, gestoppt
werden können oder sogar reversibel sind, wurde

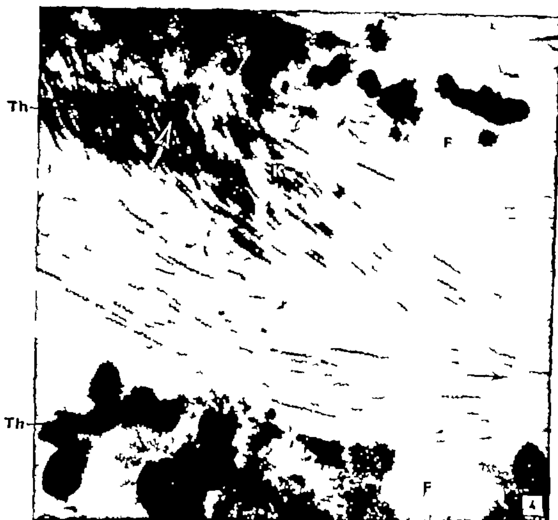


Abb 4 8 Tage nach Tubenverschluß beginnt das subepitheliale Mesenchym sich zu verdichten, durch eine enorme Produktion kollagener Fasern (*K*). *F* Fibrocyten *Th* phagocytiertes Thorotrast, das 30 Minuten vor der Tötung in den Liquor injiziert wurde nur noch wenig freies Thorotrast ist im Interzellularraum nachweisbar (↗). × 4000.

prismatischen Zellen neben langen Mikrovilli Bündel von Kinozilien, die mit typischen Basalkörperchen im apikalen Cytoplasma verankert sind (Abb 3) Daneben unterscheidet man schleimproduzierende Zellen von denen die eine Sorte elektronendichte membranbegrenzte und opake Schleimblasen in das Lumen der Paukenhöhle entleeren ander wiederum sehr helle mit staubförmigem Material beladene und nicht membranbegrenzte Blasen in das Lumen der Paukenhöhle ausstoßen Der vormals weitmaschige flüssigkeitsgefüllte subepitheliale Raum hat eine sehr starke Zunahme an kollagenen Fasern erfahren, die nun den Platz der weiten Interzellulärräume beinahe vollständig ausfüllen Insgesamt ist der subepitheliale Raum um eine Vielfaches seiner ursprünglichen Breite erweitert

Nach 8–14 Tagen erkennt man in allen Schleimhautbereichen des Mittelohres ein gleichförmiges Epithelmuster bestehend aus hochprismatischen kinozilientragenden Zellen da zwischen seröse und mukose Schleimzellen Der stark verbreiterte submuköse Raum ist von Fibrozyten und dichten kollagenen Bundeln vollständig ausgefüllt Hierdurch wird die Flüssigkeitsverschiebung innerhalb der Interzellularspalten zum Epithel hin entscheidend behindert Man kann nachweisen, daß eine in den Liquor injizierte Indikatorlösung, welche normalerweise über die bekannten Liquorabflußbahnen zu den Perilymphräumen des Innenohres und von dort



Abb. 5. 14 Tage nach Tubenverschluß. Komplett entdifferenziertes Epithel aus dem Bereich des Runden Fensters. *L*, Lumen der Paukenhöhle; *Z*, Zilientragende Epithelzellen apokrine Sekretion. 4000.

über das runde Fenster in die weiten Extrazellularräume der Mittelohrschleimhaut gelangt, nun durch die starke Bindegewebsvermehrung zurückgehalten wird und nunmehr in den wenigen, ortsweise basal gelegenen Lymphspalten nachzuweisen ist (Abb. 4). Der rege cytopemptische Flüssigkeitstransport aus dem subepithelialen Raum durch das Epithel hindurch an die Oberfläche der Schleimhaut läßt sich jetzt nicht mehr nachweisen. Der Sekretionstyp der sekretorisch aktiven Epithelzellen läßt eine apokrine und ekkrine Sekretion unterscheiden (Abb. 5, 6).

III) Um zu entscheiden, ob diese Umdifferenzierungsvorgänge des Epithels, welche zweifellos auf das Vakuum in den Mittelohrräumen nach Tubenverschluß zurückzuführen sind, gestoppt werden können oder sogar reversibel sind, wurde



Abb 6 Sekretorische Zelle mit ekkriner Sekretion (14 Tage nach Tubenverschluß) *L*, Lumen der Paukenhöhle *Th*, kondensiertes Thorotrast 11 000

In einer weiteren Versuchsserie bei 9 Meerschweinchen zur Wiederbelüftung der Paukenhöhle 20 Stunde 24 Stunden 2 Tage 4 Tage und 14 Tage nach Verödung des rechten epipharyngealen Tubenostiums das gleichseitige Trommelfell entfernt Es zeigte sich daß eine Entfernung des Trommelfells nur während der ersten 48 Stunden einen Einfluß auf die morphologischen Veränderungen der Mittelohrschleimhaut hatte Die weit geöffneten Interzellular spalten aus denen Flüssigkeit aus dem subepithelialen Raum in das Mittelohrlumen gelangte konnten sich wieder schließen. Jene Zellen die sich zu hochprismatischen Epithelzellen mit Anzeichen einer Schleimsekretion umgewandelt hatten blieben an Ort und Stelle liegen zeigten jedoch keine weiteren Veränderungen insbesondere keine nachweisbare aktive Schleimproduktion War es dagegen bereits mit einer vollständigen Umwandlung des Epithels mit einem aktiv sekretorischen Epithel gekommen so bewirkte eine auch lang dauernde Belüftung des Mittelohres keine Rückbildung des neuen Epithelmusters mehr Wurde beispielsweise 2 Tage nach Verödung des Tubenostiums das Trommelfell entfernt und die Mittelohrschleimhaut 8–14 Tage



Abb. 7. Menschliche Mittelohrschleimhaut über dem Facialiskanal (fern vom Otoskleroseherd entnommen). L, Lumen der Paukenhöhle; E, Epithelzelle, flach; F, subepithelialer Fibrocyt; K, Kollagen. 18 000.

später untersucht, so fanden wir in der Regel ausgedehnte inselförmige Areale eines hochprismatischen, kinozilientragenden und schleimproduzierenden Epithels, und im Lumen der Paukenhöhle lag über dem Epithel ein zarter Schleimfilm (Abb. 16).

IV) Die normale Mittelohrschleimhaut des Menschen unterscheidet sich in den Mittelohrregionen (Promontorium, runde Fensternische, Facialiskanal), die wir in dieser Untersuchungsreihe kontrolliert haben, nicht von der des Meerschweinchens. An keiner Stelle fanden wir schleimproduzierende Zellelemente und nur in ganz seltenen Fällen kleine Inseln von kinozilien-tragenden kubischen Zellelementen. Untersuchungen der Schleimhautverhältnisse des runden Fensters konnten wir aus verständlichen Gründen nicht durchführen (Abb. 7).

Gewebeproben von Patienten mit seröser Otitis bei undurchgängiger Ohrtrompete zeigten bei elektronenmikroskopischer Aufarbeitung die gleichen morphologischen Verhältnisse wie im Tierexperiment etwa nach 24 Stunden. Erweiterte Interzellularspalten, Eröffnung der Interzellularspalten zum Lumen der Paukenhöhle hin, Ausschleusen von untergehenden Zellresten zusammen mit Flüssigkeit in das Lumen der Paukenhöhle, sowie eine starke Aufladung des Cytoplasmas der Epithelzellen mit flüssigkeitsgefüllten Bläschen (Abb. 8). Bei chronisch fadenziehendem Paukenerguß wechselten Regionen von flachem, verklumptem Epithel mit hochprismatischem, zilientragendem schleimproduzierendem Epithel ab (Abb. 9a). In den menschlichen Schleimhautproben war vorwiegend eine apokrine Sekretion des umgewandelten Epithels zu

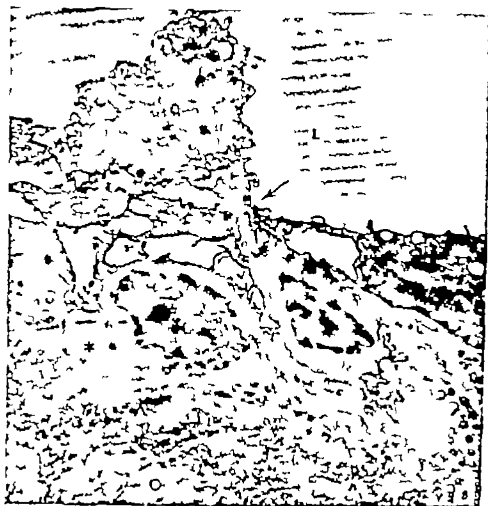


Abb. 8. Menschliche Mittelohrschleimhaut unter dem Facialiskanal bei serösem Paukenerguß. → weite, offene Interzellularspalten. ○ eiweißreiches Transsudat im Interstitium. Bm, Basalmembran. eröffneter Interzellularspalt. L, Lumen der Paukenhöhle. 18000.

erkennen (Abb. 9b). Die subepitheliale Zellage hatte stark an Volumen und Substanz zugenommen, hervorgerufen durch eine extrem starke Zunahme mesenchymaler Zellelemente. An reaktiven Zellen fanden wir häufig Histiozyten (eosinophile Leukozyten, Mastzellen und Makrophagen). bakteriologische Untersuchungen sowohl des wässrigen als auch des fadenziehenden schleimigen Paukenergusses verliefen stets negativ.

Zusammenfassung der Befunde

1. Beim Verschluß der Ohrtrompete kommt es schon nach wenigen Stunden zu einer vermehrten Passage von Extrazellularflüssigkeit durch das Schleimhautepithel hindurch in das Lumen der Paukenhöhle. Nach 24 Stunden tritt eine Ruptur der Interzellularbrücken ein und die Flüssigkeit des subepithelialen Raumes ergießt sich frei ins Lumen der Paukenhöhle.

2. Bei anhaltendem Unterdruck in den Mittelohrräumen beobachtet man eine Regeneration mit Umdifferenzierung der ursprünglichen Epithelzellen, so daß als Folge zylindrische Epithelzellen auftreten, die sich entweder als kinozilientragende Zellen oder als sekretorisch aktive Schleimzellen differenziert haben.

3. Frühzeitige Belüftung des unter Unterdruck stehenden Mittelohres kann zu einem Sistieren der epithelialen Umdifferenzierung führen, jedoch nicht zu einer Rückbildung auf den ursprünglichen epithelialen Zustand.

4. Untersuchungen an menschlichen Schleimhautproben des Mittelohres zeigen, daß die Schleimhautveränderungen bei seröser Otitis den



Abb. 9 (*a*) Menschliche Schleimhautprobe vom Promontorium bei schleimigem, chronischem Paukenerguß. Wechsel von hochprismatischem sekretorischem Epithel mit flachem Epithel. Starke subepitheliale Fibrosierung. *K*, Kapillare, *L*, Lumen der Paukenhöhle. 1250. (*b*) Elektronenmikroskopischer Ausschnitt aus Abb. 9*a*: Apokrine Sekretion heller, [illegible] Schleimblasen in das Lumen (*L*) der Paukenhöhle. 28 000.

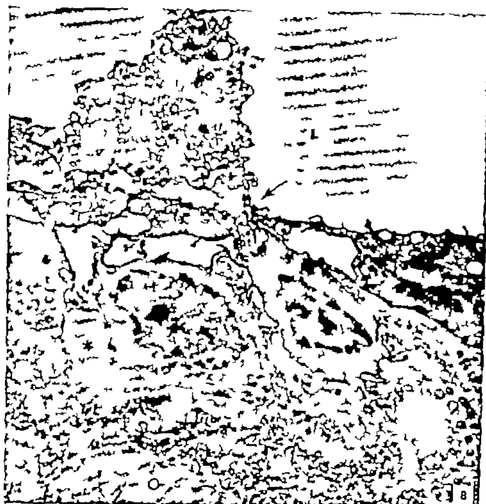


Abb 8 Menschliche Mittelohrschleimhaut über dem Facialiskanal bei serösem Paukenerguß weite, offene Interzellularspalten ○ eiweißreiches Transsudat im Interstitium *Bm*, Basalmembran ↗ eröffneter Interzellularspalt *L*, Lumen der Paukenhöhle. 18 000.

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Tabelle I. *Morphologisch definierte Stadien des Paukenergusses und die Möglichkeit seiner Beeinflussung durch Belüftung des Mittelohres (B Paracentese, Paukenröhrchen)*

	Morph. Kennzeichen	Konsistenz	Belüftungserfolg
Stadium 1	Erhöhte Pinocytose-aktivität der Epithelzellen, Verbreiterung des submucösen Raumes	Wässrig	Positiv
Stadium 2	Ruptur der Interzellularspalten, Entweichen von subepithelialer Flüssigkeit, Gefässweitstellung	Wässrig	Positiv
Stadium 3	Epithelmetaplasie, echte Schleimzellen übernehmen eigenständige Funktion, Bindegewebshyperplasie der Submucosa	Fadenziehend, hoch viscös	Geringe Beeinflussung der selbständigen Schleimsekretion durch Belüftungsmassnahmen

gleichen Gesetzen unterworfen sind wie sie sich im Tierexperiment reproduzieren lassen (Tabelle I).

DISKUSSION

Bei ausbleibendem Druckausgleich in den Mittelohrräumen, dessen Ursache entweder in Veränderungen im Bereich des Epipharynx oder im Tubenverlauf zu suchen sind, entsteht in zunehmendem Maße ein Unterdruck in den Mittelohrräumen. Die dabei auftretenden physikalischen Kräfte wirken durch Zug an den Wänden dieses Raumes. Dieser Zuge bewirkt einen zunehmenden hydrostatischen Druck im Bereich der Extrazellularflüssigkeit der Submucosa, der bald so stark sein wird, daß er die epithelialen Interzellularfugen sprengt, wodurch subepitheliale Flüssigkeit in das Lumen der Paukenhöhle austritt. Zuvor schon kommt es zu einer ultrastrukturell sehr deutlich erkennbaren Zunahme einer cytopemptischen Tätigkeit der Epithelzellen. In vermehrtem Maße wird Flüssigkeit des subepithelialen Raumes zur Oberfläche der Epithelzellen geschleust und dort ausgestoßen (Arnold, 1972). Die Ursache des zunehmenden Unterdruckes in den Mittelohrräumen bei verschlossener Tube und intaktem Trommelfell liegt nun darin, daß sich das Gasgemisch in den Mittelohrräumen, bestehend aus Sauerstoff, Stickstoff und Kohlendioxyd mit den gleichen Gasen im Gewebe auseinandersetzt und einen Ausgleich des Partialdruckes „Gasgemisch-Mittelohrräume" und „Gasgemisch-Gewebe" zu erreichen sucht. Da der Partialdruck der im Mittelohr befindlichen Gase mit Ausnahme des CO_2 höher ist als der im Gewebe, diffundiert ständig Stickstoff und Sauerstoff in das Gewebe hinein. Dadurch entsteht durch Abnahme der Gesamtgasmenge in den Mittelohrräumen bei gleichbleibendem Mittelohrvolumen ein Unterdruck (Feldmann, 1973), der nach Erschöpfen der Elastizitätskraft des Trommelfelles und der anderen beweglichen Membranen des Mittelohres (runde Fenstermembran, ovales Fenster) auf ein starres System einwirkt. Dadurch wird Flüssigkeit aus dem wasserreichen Mucoperiost an die Oberfläche gesaugt, wobei sich nach einer ursprünglichen Weitstellung der Kapillaren der Submucosa auch ein Gefäßtranssudat beimischt, an dem Austritt von Erythrozyten in die Submucosa wird erkenntlich, daß es in zunehmendem Maße auch zu einem Exsudat kommt (Arnold, 1972). Der fortbestehende hydrostatische Druck der Submucosa bewirkt schließlich die Ruptur der epithelialen Kittleisten, wodurch die Flüssigkeit des subepithelialen Raumes, bestehend aus Extrazellularflüssigkeit, Transsudat bzw. Exsudat in das Lumen der Paukenhöhle strömt. Dieses wässrige Ergußmedium zeigt auch biochemisch große Ähnlichkeit mit

Blutserum und Lymphflüssigkeit (Juhn et al., 1971 Tönder et al., 1971).

Unterdruck im Paukenlumen, Schädigung der Epithelzellen durch Ruptur ihrer Interzellularbrücken, starke Aufladung mit Extrazellularflüssigkeit führen offensichtlich zu einer Umdifferenzierung der Epithelzellen. In zunehmendem Maße wandeln sich die ursprünglich flachen Epithelzellen in hochprismatische, zilientragende Zellen um, andere wiederum lassen insbesondere in ihrem apikalen Zellbereich cytoplasmatische Neubildungen erkennen, die auf eine sekretorische Aktivität hindeuten. Eine Belüftung der Pauke im Frühstadium vor Beginn des epithelialen Umbaues bewirkt durch Verschluß der Interzellularspalten ein Sistieren des serösen Ergusses und verhindert sichtlich die Metaplasie des Epithels. In einem späteren Stadium werden die bereits angelaufenen Umbauvorgänge zwar aufgehalten, können aber nicht zu einer Rückbildung des bereits umdifferenzierten Epithels führen. Auch eine lang andauernde Belüftung hat jetzt keinen Einfluß mehr auf die neuen Schleimhautverhältnisse.

Verschiedene Untersuchungen menschlicher Schleimhauterkrankungen des Mittelohres, beispielsweise beim idiopathischen Hämatotympanon (Arnold & v. Ilberg, 1974) oder bei der otosklerotisch veränderten Mittelohrschleimhaut geben zu erkennen, daß eine alleinige Lymphostase im Subepithel, die mit einer starken Bindegewebsvermehrung und Einengung der extrazellulären Lymphbahnen einhergeht, offensichtlich ebenfalls bestimmte Epithelveränderungen bewirkt. dabei kommt es an verschiedenen Stellen der Mittelohrschleimhaut zu inselförmigen Ansammlungen von kinozilientragenden, hochprismatischen Zellen. Schleimzellen jedoch, wie sie als typisch für ein lang anhaltendes Serotympanon oder Mucotympanon bekannt sind, werden bei diesen Erkrankungen nicht nachgewiesen. Das Auftreten von schleimproduzierenden Zellen im Mesotympanon bei chronischem Paukenerguß würde nach unseren Befunden ausschließlich eine Folge des chronischen Reizzustandes (erhöhter Unterdruck in den Mittelohrräumen, starke Flüssigkeitsaufladung der Epithelzellen) sein, wogegen kinozilientragende Zellelemente ihre Entstehung offensichtlich auf mehrere Faktoren zurückführen lassen.

Injiziert man zu einem Zeitpunkt, wo sich das Epithel bereits umdifferenziert hat und eine neue Funktion übernommen hat, Thoriumdioxyd in den Liquor, so kann dieses nicht wie üblich bis zum Epithel der Mittelohrschleimhaut vordringen, sondern hält sich infolge der erheblichen subepithelialen Fibrosierung nur noch in schmalen Lymphbahnen in der Tiefe der Submucosa auf. Diese submukösen Veränderungen, welche sowohl bei den experimentellen Untersuchungen beim Meerschweinchen wie auch bei den menschlichen Schleimhautproben deutlich wurden (die enorme Verbreiterung des subepithelialen Raumes, die bindegewebige Zunahme und die damit verbundene Einengung der ursprünglich weiten Extrazellularräume) sind die Erklärung dafür, daß bei zusätzlichen bakteriellen Infektionen, die sich ja klinisch häufig bei chronisch schleimproduzierenden Mittelohren einstellen, so selten eine Überleitung zum Labyrinth vorkommt. Offensichtlich stellt das aktiv schleimproduzierende Epithel mit seinem Oberflächenschleimfilm und der Kinozilienbewegung (Lim et al., 1972) zusammen mit dem stark bindegewebig verdichteten subepithelialen Raum eine ausgezeichnete Barriere gegen eindringende Keime dar. Hinzu kommt die erstaunliche Fähigkeit der Fibrozyten, sich sehr schnell auf verschiedenartige Reize einzustellen und Makrophagentätigkeit oder histiozytäre Aufgaben zu übernehmen (Arnold & v. Ilberg, 1974). Nach Untersuchungen von Tomasi et al. (1968) und Mogi et al. (1973) enthält der Schleim der umgebauten Epithelzellen reichlich lokale Immunglobuline, so daß die „Schutzwirkung" des neu gebildeten Epithels zusätzlich erhöht wird.

SUMMARY

1. Tubal obstruction causes a rapid rise in transepithelial cytopempsis. The squamous epithelial cells show numerous vesicles carrying subepithelial fluid (extracellular fluid) to the middle ear cavity. 24 hours following tubal obstruction widespread rupture of the epithelial junctions can be observed. Subepithelial fluid, consisting of

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lymphfluid, transudate and later exsudate, enters the middle ear cavity without passing a cellular barrier

2 Long lasting negative pressure provoces a cellular differentiation (metaplasia!) of the formerly squamous epithelium to a high cylindric cell layer with new functions cillary movement and secretory activity

3 Ablation of the tympanic membrane to expose the middle ear to air after 2–4 days, causes a stop in the epithelial differentiation but no regeneration to the normal histological flat formation

4 Studies of samples of human middle ear mucosa in serous otitis or sero-mucous otitis show exactly the same results as during the different stages of our animal experiments.

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Acta Otolaryngol Suppl 330 64-67 1975

SIMULTANEOUS APPLICATION OF ELECTRONYSTAGMOGRAPHY (ENG) AND PHOTOELECTRONYSTAGMOGRAPHY (PENG) IN THE CASE OF THERMAL LABYRINTH EXAMINATION[1]

J Wilke K. H Gramowski and H Gobsch

From the Throat Nose-Ear-Clinic of the Medical Academy Erfurt DDR

Abstract At examination of normal persons, the ENG registration method was compared with that of PENG Special examinations were executed with regard to the behaviour of the beat rates during the culmination phase of thermal labyrinth reactions by using each of both registering methods. By synchronous recording of PENG and ENG it was possible to settle the discrepancy of the greater number of beats in ENG compared with those of PENG while the examinations were executed at different times. The PENG-method does not exclude an optical fixation due to the necessary interior illumination, and thus results in a retarding of the reaction and smaller beat rates. This fact should be considered when comparing the results of ENG and PENG

In order to carry out nystagmus recordings, we have applied both the ENG and the PENG methods. By registering the thermal labyrinth reactions of normal persons, we pointed out that in the electronystagmogram (ENG) the number of the nystagmus beats was greater than in the photoelectronystagmogram (PENG) it must be noted that registration was not executed simultaneously but in sequence Due to the greater number of beats in ENG than in PENG the problem again arose where on application of ENG potential variations could also be retarded in connection with the occurrence of genuine nystagmus. Although they give the impression of being nystagmus beats in the recording, they do not correspond to nystagmus occurrence in reality

We have already referred to the possibility (Gramowski, 1962, 1964 1965) that when applying the ENG method nystagmus-like disturbance variables sometimes may be recorded together with genuine nystagmus occurrence, thus making an exact evaluation questionable.

Frenzel s finding is worthy of mention in this regard. He was able to plot a "nystagmus curve when examining a bilaterally blind man whose right eye was enucleated and whose left eye was only a diminutive, contracted bulbus, so that the normal dipol relations did not exist.

When applying the PENG method, we can take it for certain that the nystagmus recordings we registered are an exact copy of the real movements of the eyes Thus it seemed obvious to examine the state of increased beat rates in the ENG by simultaneous PENG registration

Synchronous recording of thermal labyrinth reactions in normal persons by ENG and PENG enabled us to probe the ENG-method critically

MATERIAL AND METHODS

The comparative examinations were made with normal persons, i e otoneurologically healthy probands. The thermal irritation was caused with 20 ml of water at a temperature of 30 C During the examination the patient was in lying position with his head about 30 above the horizontal.

The application of the PENG method was made possible by using original PENG-spectacles, according to Gestewitz. This permits simultaneous measurement of both eyes and the registering of their movements the horizontal and the vertical components can be registered

[1] Devoted to Prof Fukuda on the occasion of his returning as Director of the Department of Otolaryngology Gifu University School of Medicine.

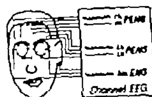


Fig. 1 Scheme for the synchronous recording of a thermal labyrinth reaction (left ear was irrigated with 20 ml of water 30 C).

eparately The proband's eyes are illuminated hrough a red filter thus excluding fixation and dazzle, as far as is possible. By an infrared reflecting disc which is transparent and by optical means, the reflected light reaches the photoelectric transducers. These have an internal resistance of 10–20 kΩ, divided in 4 equal sectors, and provide each of the vertical and horizontal components of the eye movements with peak to-peak voltage

For registering the relatively small measured quantity of about 100 μV/30° of eye deviation, we have used an 8-channel EEG-device produced by VEB Messgerätewerk Zwönitz as previously recommended by Gestewitz (1965).

With this measuring device and after having carefully adjusted the optical system and calibrated the angle of view all clear registering of the nystagmus occurrence could be realized without further problems.

The routine recording of the ENG was done by an electronystagmograph from Tönnes (Freiburg/Breisgau). Some of the technical characteristics of the ENG device differ considerably from those of the EEG device, and the recording of ENG was therefore executed with the aid of the EEG device This was especially practised in order to obtain synchronous recording by ENG and PENG Concerning the above we state that due to the relatively small initial impedance of the EEG device of about 800 kΩ, the ENG recording is rather problematic because the corneo-retinal potentials have the size of only 100 μV/30° of eye deviation. The required increase of ENG registering inevitably involves a *higher interference* level which, however can be limited sufficiently by a good arrangement of shielding and earthing. With the EEG device, the separate plottings of ENG and PENG raised almost no objects, though synchronous *recording was rather problematic* because, in addition to the preparations for PENG registering, two electrodes had to be placed and fixed to the palpebral angles under the spectacles (Fig. 1).

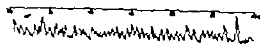


Fig ENG recording during the culmination phase of thermal labyrinth reaction (left ear was irrigated with 20 ml of water, 30 C).

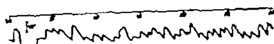


Fig 3. PENG recording during the *culmination phase* of thermal labyrinth reaction. Recording with proband's eyes open and illuminated by PENG red light. The *proband was the same as in Fig. 2*, as also was the part of curve.

With regard to the comparative examinations of the ENG and PENG methods, we generally restricted ourselves to recording the horizontal components of nystagmus.

RESULTS

The accompanying figures show the reaction curves registered at the examination of one proband. Fig. 2 is a part (culminations phase) of a thermal labyrinth reaction where the ENG-method was used. Registration was carried out

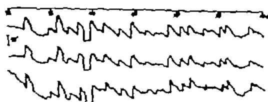


Fig 4 Synchronous recording of ENG–PENG during the culmination phase of thermal *labyrinth reaction* (left ear was irrigated with 20 ml of water 30 C). Recording with proband' eyes open and illuminated by PENG red light. Curve 1 PENG of right eye. Curve 2 PENG of left eye. Curve 3 ENG of both eyes. The proband was the same as in Figs. 2 and 3.

while the proband s eyes were open, but in a dark room Thus any fixation was completely impossible During the chosen interval of 30–60 seconds after having applied an irritation 51 beats were registered (Fig. 2)

Fig. 3 shows another part of the nystagmus reaction in the same proband The irritation modus was the same as in case shown in Fig. 2, namely irrigation on the left side with 20 ml H_2O of 30 C. The thermal labyrinth reaction *however* was recorded with the aid of the PENG spectacles *ad modum* Gestewitz. During the plotted time interval of 30–60 seconds, only 32 beats were registered but it must be noted that this registration was executed in a dark room with the proband s eyes open though the eyes were illuminated by red light as required by the PENG spectacles (Fig. 3)

Fig. 4 shows the synchronous recording of a thermal labyrinth reaction by PENG and ENG with the same proband and with the same irritation (Fig. 4) Here we have to state that in each ENG and in each PENG the same number of beats have been recorded (32 beats during the appointed time interval) Again, registering was executed with the proband s eyes open and under PENG-illumination In ENG and PENG not only the number of beats, but also their form are almost identical.

DISCUSSION

At first, the question arose whether the same beat rates could be received by simultaneous application of PENG and ENG in the course of a thermal labyrinth reaction. This question can be answered in the affirmative The increased beat rates in the separate ENG (Fig. 2) in comparison with those in PENG (Fig. 3), under separate examination conditions, can be explained by extravestibular influences when applying the ENG method With the ENG method (open eyes, dark room) a fixation of the eyes is almost impossible whereas with the PENG method, a part fixation has to be taken into account from the very beginning. This part fixation will cause a retardation of the nystagmus reaction and result in a smaller number of beats.

When comparing the results of examinations obtained by ENG and by PENG one must consider that when applying the PENG-method, one has to put up with a certain influence from optical fixation

The synchronous recording of nystagmus reactions by PENG and by ENG have proved that when registering with the aid of ENG, recordings are obtained which correspond to those of PENG provided that the same recording conditions that are required in case of PENG application are applied. This statement by no means negates the critical hints concerning the ENG method (Gramowski, 1964 1965 Jongkees, 1965 Megighian & Waldecker 1961 Schaffrath, 1965) Nevertheless, when analysing ENG recordings foreign potentials such as disturbance variables and possible sources of error have to be considered and thus the interpretation of ENG results is problematic if it is done by inexperienced colleagues.

In the case of PENG application, there are no modifications in the nystagmus recordings caused by foreign potentials of different origin, though a certain rate of nystagmus retarding optical fixation cannot be excluded If there is any doubt concerning the interpretation of ENG-curves, it is useful to carry out a synchronous recording by ENG–PENG

ZUSAMMENFASSUNG

In Untersuchungen an Normalpersonen wurde das ENG mit dem PENG-Registrierverfahren verglichen. Speziell untersucht wurde das Verhalten der Schlagzahlwerte während der Kulminationsphase thermischer Labyrinthreaktionen bei Anwendung beider Registrierverfahren. Durch synchrone Aufzeichnung des PENG und des ENG konnte die Diskrepanz zwischen den höheren Schlagzahlen im ENG gegenüber PENG bei zeitlich getrennten Untersuchungsgängen geklärt werden. Bei der Anwendung des PENG-Verfahrens ist eine optische Fixation infolge der notwendigen Innenbeleuchtung nicht auszuschließen, wodurch eine Hemmung der Reaktion und daher geringere Schlagzahlwerte bei diesem Verfahren auftreten. Diese Tatsache sollte beim Vergleich von ENG- und PENG-Ergebnissen berücksichtigt werden.

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Acta Otolaryngol Suppl 330 68–71 1975

THE EFFECT OF GRAVITY ON GALVANIC NYSTAGMUS IN RABBITS

T Swaak and W J Oosterveld

From the Department of Otolaryngology University of Amsterdam Amsterdam, The Netherlands

Abstract The effect of gravity on a galvanic nystagmus provoked in rabbits was investigated. Weightlessness increased the amplitude but decreased the frequency as well as the speed of the nystagmus. During continuous galvanic stimulation the provoked nystagmus disappeared spontaneously after a period of 60–120 seconds. Weightlessness was able to arouse this nystagmus again. An explanation of this phenomenon might be that galvanic nystagmus undergoes a modifying effect from the vestibular maculae and their state of stimulation.

Galvanic stimulation of the ear can provoke nystagmus (Brünings, 1911). This stimulation can be performed in several ways (Bellens, 1950) The size of the electric power required for the elicitation of galvanic nystagmus depends strongly on the method of stimulation If this method of stimulation is bipolar bi-auricular the necessary strength of the electric current is the lowest With galvanic stimulation in humans Hennebert (1950) found that at least 2–3 mA was necessary to elicit nystagmus This is in accordance with the findings of Hahn & Menzio (1966), however Pfaltz & Richter (1965) described a galvanic nystagmus in humans when they were stimulated with a current of 1–2 mA only

A galvanic nystagmus starts with an eye deviation to the side of the anode Stimulation with a pulsating galvanic current provokes a sinusoidal eye movement which oscillates in direct relation to the frequency of the pulsating current The amplitude of the eye deviation is related to the strength of the electric current A parallel swing gives similar eye movements to the subjects

In a previous study we described that—when both methods of stimulation are applied at the same time—the effects of both stimulations are summated algebraically (Swaak 1974) (Fig. 1)

In order to provoke a galvanic nystagmus in rabbits, a direct current of at least 1–5 mA must be applied The nystagmus caused in this way extinguishes within 60 seconds. In order to provoke a nystagmus with a constant frequency and a duration of more than 60 seconds, the current must be at least 10 mA.

The aim of this study is to investigate the effect of gravity on galvanic nystagmus in rabbits

METHODS

Experiments were performed in four rabbits. These rabbits were purebred laboratory animals (hollanders) with a weight of about 2 000 g each. In order to immobilize the animal it was tied to a rabbit holder and strapped with bandages.

Needle electrodes for the galvanic stimulation were applied in such a way that the stimulation could be given bipolar bi-auricularly The equipment for photonystagmography was mounted on the rabbit holder in such a way that movements of the left eye could be recorded (Fig. 2). Photonystagmography is the method of choice for galvanic nystagmus, since a galvanic current has a disturbing effect on electronystagmographic recordings. An electric current of 5–10 mA was applied in order to elicit a galvanic nystagmus. Increased g values, as well as weightlessness were evoked in an airplane Fokker F27 of the Royal Dutch Airforce As described in previous papers (Oosterveld, 1969) weightlessness could be achieved in periods from 5 up to 12 seconds when the airplane was performing

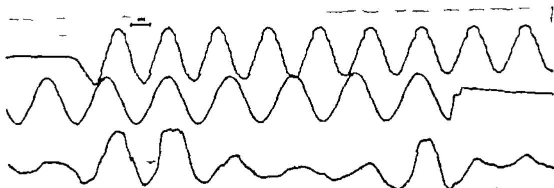


Fig 1 A rabbit is stimulated by both an oscillating linear acceleration and an oscillating galvanic current. The oscillation times of both stimulations differ a little. The oscillating linear acceleration is applied by means of parallelswing. The rabbit is swung sideways. The recordings represent. (1) the movements of the parallel-swing, (2) the sinusoidally oscillating galvanic current, (3) eye movement of the rabbit in the vertical plane.

parabolic flight. The weightless periods were preceded as well as followed by periods of approximately 10–15 seconds during which the g-load in the Z axis was increased up to 2.5 g.

Galvanic nystagmus was provoked in periods during which the galvanic nystagmus remained constant in speed and frequency. These periods lasted up to 120 seconds. In each period several paraboles were flown. With each rabbit the ex periments were flown several times.

RESULTS

In the first period with increased g-value in the pull-up of the parabola the galvanic nystagmus showed an increase in frequency and speed

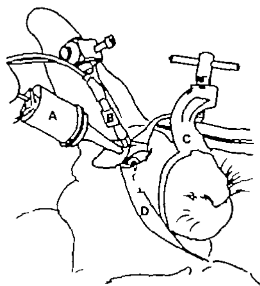




Fig 2 (A) Infrared light source, (B) probe for photo-nystagmography (C) rabbit holder, (D) ropes and clamp hels keep the eye open.

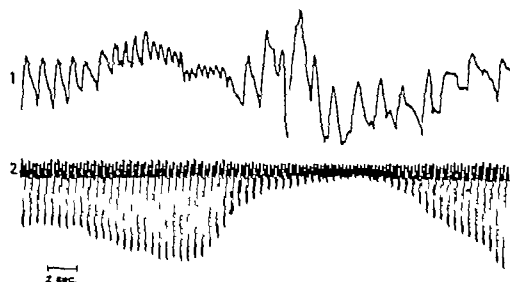


Fig 3 The effect of g-loading on galvanic nystagmus. The recording of the left eye of the rabbit is represented by 1 The g-load in the Z-axis is shown in curve 2. Before the weightless period the g load increases to 2 g. As soon as the value of g goes up the frequency of the nystagmus increases, while the amplitude decreases. In weightlessness the frequency decreases, while the amplitude increases.

(Fig. 3). In the weightless interval in the push over the frequency of the nystagmus decreased but the amplitude increased. In the second period with increased g, in the pull-out of the parabola, the galvanic nystagmus showed up again.

The increase as well as the decrease in nystagmus frequency and amplitude seize was found to be without any measurable latency

If weightlessness was introduced during galvanic stimulation but after the nystagmus had

Fig 4 In A and B the upper tracings show nystagmus beats which appeared during weightlessness in two rabbits. After galvanic stimulation had been applied for a period of more than 120 seconds, the nystagmus stopped spontaneously In the period of weightlessness the nystagmus reappeared.

stopped (which happens 60–120 seconds after the onset of acceleration) the galvanic nystagmus reappeared (Fig. 4). The increasing g in the pull-out of the parabola made it fade away again. In other experiments performed in the rabbits no nystagmus could be elicited by differences in the g-load if galvanic stimulation had not been given before.

CONCLUSION

In a previous study we proved that weightlessness as well as increased g-values have a strong effect on positional alcohol nystagmus (Oosterveld, 1970).

Increase of g-value enhances the speed of the slow component of PAN. Just after PAN has disappeared, increase of the g-values makes the nystagmus reappear (Oosterveld, 1969).

In weightlessness PAN I as well as PAN II fade away. Similar results were found for the effect of gravity on caloric vestibular nystagmus. Rotational nystagmus elicited in the weightless state in rabbits proved to increase in amplitude and frequency. The effect of increased gravity on galvanic nystagmus is in agreement with this, in contrast with the observation on caloric and alcohol nystagmus, weightlessness can bring a galvanic nystagmus back.

An explanation of this phenomenon might be that galvanic nystagmus undergoes a modifying effect from the vestibular maculae and their state of stimulation. When the maculae are not stimulated by any gravitational acceleration, the vestibular system increases its responses to a rotation acceleration. The same seems to happen to the phenomen of the galvanic stimulation.

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Reprint requests to:

W J Oosterveld M.D
Wilhelmina-Gasthuis
Amsterdam
The Netherlands

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SUR LA PROBABILITÉ, CHEZ L HOMME EN ORTHOSTATISME, DE VOIES FONCTIONNELLES VESTIBULO-OCULO-NUCO-SPINALES JOUANT UN RÔLE DANS LA MISE EN PLACE ET LE MAINTIEN DU CENTRE DE GRAVITÉ DU CORPS DANS LE POLYGONE DE SUSTENTATION

Etude Statokinésimétrique

J B Baron N Ushio M Gregoric, T Mano J Noto G Bizzo P M Gagey J C Bessineton et M Pacifici

Centre Psychiatrique Sainte-Anne Paris France

Lors du Second Symposium International de Posturographie de Smolenice, après la communication de G Bizzo (1973) sur les *stimulations galvaniques* labyrinthiques et celle de P M Gagey (1973) sur les variations de tonus au niveau des membres inférieurs induits par les mouvements de la tête et des yeux, nous avons été amenés à discuter avec les professeurs V S Gurfinkel (1973)[1] et M Alexeef (1973)[1] sur les rapports existant entre la direction des déplacements de l axe du corps à la suite de stimulations galvaniques labyrinthiques et le changement de position de la tête et des globes oculaires. Nous regrettions alors dans cette discussion l absence du professeur T Fukuda (1957) dont les travaux dans ce domaine font autorité reprenant sous un aspect original les travaux fondamentaux de Magnus (1924) sur les réflexes toniques posturaux.

A mon retour en France, séduit par ce thème de recherches, mon équipe à laquelle s était associée N Ushio[2] déjà sensibilité à ces problèmes par ses maîtres M Hinoki (1971), T Fukuda & D Nonaka (1954) se mettait au travail sur cette étude Sur ces entrefaits deux neurologues T Mano[3] et M Gregoric[4] étant venus dans mon service pour un bref séjour de travail se joignaient à nous, apportant leur expérience des réflexes T et H

MATERIEL ET METHODE

7 jeunes pompiers volontaires, d âge variant de 18 à 20 ans, ont participé à l expérience dans les conditions suivantes

1 *Etude statokinésimétrique*

Le sujet debout sur la plateforme détectrice du statokinésimètre dans une pièce obscure regarde 1) soit droit devant lui une barre fluorescente placée dans le plan médian de son polygone de sustentation 2) soit un point lumineux de 2 mm placé à un mètre à 45

Il reçoit à travers une électrode mastoïdienne positive et une électrode controlatérale *négative* au poignet un courant galvanique de 0 5 *mA* 6 stimulations rectangulaires de 4 *secondes chacune*, séparées stochastiquement *par des intervalles* de 10 à 15 secondes sont appliquées pour chaque essai La stimulation déclenche le balayage d un analyseur multicanaux à mémoire fonctionnant comme un moyenneur qui enregistre les déplacements stabilographiques Avant/

[1] Chaires de la Transmission de l'Information à Moscou (URSS).
[2] Assistant d oto-rhino-laryngologie de la Faculté de Médecine de Tokushima, Japon.
[3] Assistant de neurologie à Nagoya, Japon.
[4] Assistant de neurologie à Ljubljana, Yougoslavie.

Arrière et Gauche/Droite des informations provenant du statokinésimètre.

Les conditions expérimentales sont les suivantes

A. Le sujet à la tête fixe (plan sagittal perpendiculaire à l'horizontale). Il regarde la barre lumineuse.

B. Le sujet à *la tête mobile (plan sagittal tourné à 70° sur l'horizontale). Il ne regarde plus la barre lumineuse mais tourne sa tête soit à* droite soit à gauche de telle sorte que la mastoïde portant l'électrode positive se trouve soit vers l'avant soit vers l arrière.

C Le sujet à la tête fixe (plan sagittal) perpendiculaire à l'horizontale). Il regarde le point lumineux situé soit du même côté soit du côté opposé à la mastoïde portant l'électrode positive.

D Le sujet à la tête mobile (plan sagittal incliné de 45° sur l'horizontale). Il regarde la barre lumineuse et incline sa tête soit du même côté soit du côté opposé à la mastoïde portant l'électrode positive.

Dans ces différentes conditions expérimentales, une première série d examens est pratiquée le pôle positif placé à la mastoïde droite, une seconde série, le pôle positif à la mastoïde gauche.

II. *Etude du réflexe H et T*

L étude du *réflexe* H *se fait* avec un stimulateur et un électromyographe DISA (2 canaux, type 14 1 21).

L étude du réflexe T se pratique a ce un marteau mobile sur une potence équipé d un *accéléromètre déclenchant le balayage d un* oscilloscope (*TEKTRONIX 5103 N*).

Les conditions expérimentales sont les suivantes le sujet étant couché sur le ventre

A. La tête fixe (plan sagittal perpendiculaire à l'horizontale), il regarde soit droit devant lui, soit à droite puis à gauche à 45

B. La tête mobile (plan sagittal tourné à 45 *sur l'horizontale*), il tourne la tête à droite puis *à gauche en regardant dans la direction du dé placement céphalique.*

Chaque essai est pratiqué *sur la jambe droite* puis sur la jambe gauche.

Pour le réflexe T 10 stimulations sont appliquées et sommées. Pour *le réflexe H, 10 groupes* de 2 stimulations séparées *de 50, 100, 150,* 200, 300 ms sont délivrées *et sommées.*

RESULTATS

I *Etude statokinésimétrique*

1 *Dans la situation A.* La stimulation galvanique électrique labyrinthique provoque un déplacement latéral du centre de gravité du corps du côté du pôle positif (Fig. 1A). Nous avons montré antérieurement (Bizzo & Baron, 1972) que ce déplacement était proportionnel à l'intensité du courant pour des valeurs comprises entre 0,25 et 0 75 mA. La stimulation provoque *un effet facilitateur du tonus des muscles abducteurs de la cuisse, tenseur du fascia lata homolatéral*) au pôle positif Ce qui semblerait prouver l'existence d'une voie fonctionnelle *vestibulo-spinale jouant* sur le motoneurone des abducteurs, adducteurs des membres inférieurs et particulièrement du tenseur du fascia lata.

2. *Dans la situation B* La stimulation galvanique électrique labyrinthique provoque un déplacement antérieur ou postérieur du centre de gravité du corps du côté du pôle positif (Fig. *1B). La rotation de la tête changeant la répartition tonique entre les muscles nucaux droits* et gauches ainsi que sur leurs tendons et les ligaments de l'articulation nucale change la direction du déplacement du corps induit par la stimulation. C'est le tonus des muscles fléchisseurs ou extenseurs des membres inférieurs qui est *facilité* bilatéralement suivant la position de la tête ce qui semblerait mettre en évidence une voie fonctionnelle nuco-spinale jouant sur *les différents motoneurones* des muscles fléchisseurs, *extenseurs des membres inférieurs.*

3. *Dans la situation C La stimulation* galvanique électrique labyrinthique *provoque un dé*placement latéral du centre de gravité du corps d une amplitude inférieure à celle obtenue lorsque la tête est droite (situation A) (Fig. 1C). La déviation des globes oculaires change la répartition tonique entre les muscles moteurs *oculaires abducteurs*, adducteurs droits et *gauches ainsi qu'*entre leurs tendons entraînant

une diminution du déplacement du centre de gravité du corps d autant plus marquée que la déviation des globes oculaires est opposée au pôle positif C'est le tonus des muscles abducteurs, adducteurs, des membres inférieurs qui est inhibé en fonction des variations de tonus des muscles moteurs oculaires ce qui semble mettre en évidence une voie fonctionnelle oculomotrice spinale jouant sur les différents motoneurones des muscles abducteurs, adducteurs des membres inférieurs.

4 *Dans la situation D* La stimulation galvanique électrique labyrinthique provoque un déplacement latéral du centre de gravité du corps d une amplitude inférieure à celle obtenue lorsque la tête est droite (situation A) (Fig. 1D) Cette diminution est d autant plus marquée que la déviation de la tête est opposée au pôle positif elle est soit inférieure à la situation C si la déviation de la tête est opposée au pôle positif soit supérieure si la déviation de la tête est du même côté que le pôle positif La déviation latérale de l axe de la tête change la répartition tonique entre les muscles profonds droits et gauches de la nuque ainsi qu entre leurs tendons et les ligaments de l articulation nucale entraînant une diminution dans le déplacement du centre de gravité du corps. C'est le tonus des muscles abducteurs, adducteurs des membres inférieurs qui est inhibé en fonction des variations de tonus des muscles de la nuque droits et gauches ce qui semble mettre en évidence une voie fonctionnelle nuco-spinale jouant sur les différents motoneurones des muscles abducteurs, adducteurs des membres inférieurs.

Il est à noter que dans les situations B et D un maintien correct de la tête dans la position imposée est indispensable pour l obtention d une réponse caractéristique

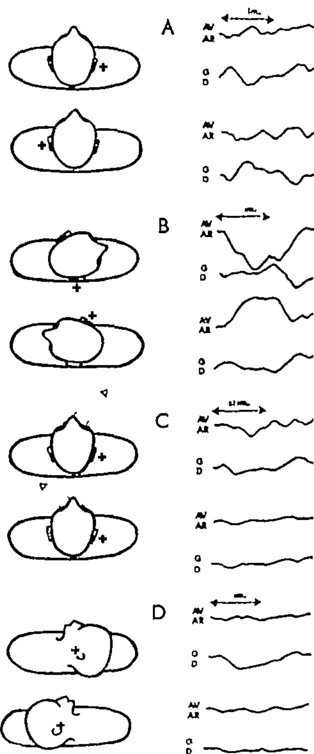


Fig 1 Etude statokinésimétrique des déplacements du centre de gravité du corps d un sujet recevant une stimulation gal anique labyrinthique de 0,5 mA pendant 4 secondes. (A) Stimulation seule; (B) stimulation rotation de la tête; (C) stimulation + rotation des yeux, (D) stimulation inclinaison de la tête

II *Etude du réflexe H et T*

De nos résultats préliminaires il ressort que les réflexes H et T varient d amplitude en sens inverse suivant les variations de tonus des muscles nucaux et des muscles oculaires. Cette variation est asymétrique entre la jambe droite et la jambe gauche (Fig. 2)

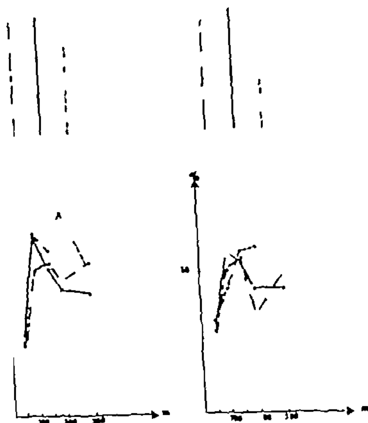


Fig. 2. Etude des réflexes T et H sur la jambe droite d'un sujet après mesure des résultats oscillographiques des réponses électromyographiques lorsque la tête ou les yeux sont tournés à droite (*D*, — —), à gauche (*G* — — —), ou lorsqu'ils sont en position de repos (0, —).

CONCLUSION

…ensemble de ces faits, dans nos conditions …mentales, il résulte que dans la mise en … et le maintien de la projection du centre …ravité du corps à l'intérieur du polygone …ustentation un certain nombre de systèmes …ori-moteurs rentre en jeu.

…) un système vestibulo-spinal *parfaitement* …u et bien isolé dans sa réponse à la stimu…on galvanique intéressant le fonctionnement … muscles abducteurs et adducteurs des mem…s inférieurs.

b) un système nuco-spinal concernant le …ctionnement des muscles abducteurs, adduc…rs et fléchisseurs, extenseurs des membres …érieurs.

(*c*) un système oculo-spinal se rapportant au fonctionnement des muscles abducteurs, adducteurs des membres inférieurs.

Ces deux derniers systèmes modulent par leur effet facilitateur ou inhibiteur les réponses de la stimulation galvanique labyrinthique. Ils pourraient avoir comme point de départ soit les terminaisons annulospiralées musculaires soit *des organes golgiens tendineux ou ruffiniens* ligamentaires.

Des études en cours permettent d'aborder le mode d'action de ces différents systèmes. L'étude des réflexes H et T lors des changements de la position de la tête ou des globes oculaires localiserait le point d'impact des voies nuco-spinale et oculo-spinale au niveau médullaire. Leur variation semblerait impliquer une action

une diminution du déplacement du centre de gravité du corps d autant plus marquée que la déviation des globes oculaires est opposée au pôle positif C'est le tonus des muscles abduc teurs, adducteurs, des membres inférieurs qui est inhibé en fonction des variations de tonus des muscles moteurs oculaires ce qui semble mettre en évidence une voie fonctionnelle oculomotrice spinale jouant sur les différents motoneurones des muscles abducteurs, adducteurs des *membres inférieurs.*

4 *Dans la situation D* La stimulation galva nique électrique labyrinthique provoque un dé placement latéral du centre de gravité du corps d une amplitude inférieure à celle obtenue lorsque la tête est droite (situation A) (Fig. 1 D) Cette diminution est d autant plus marquée que la déviation de la tête est opposée au pôle posi tif elle est soit inférieure à la situation C si la déviation de la tête est opposée au pôle positif soit supérieure si la déviation de la tête est du même côté que le pôle positif La déviation latérale de l axe de la tête change la répartition tonique entre les muscles profonds droits et gauches de la nuque ainsi qu entre leurs tendons et les ligaments de l articulation nucale entrai nant une diminution dans le déplacement du centre de gravité du corps. C'est le tonus des muscles abducteurs, adducteurs des membres inférieurs qui est inhibé en fonction des varia tions de tonus des muscles de la nuque droits et gauches ce qui semble mettre en évidence une voie fonctionnelle nuco-spinale jouant sur les différents motoneurones des muscles abducteurs, adducteurs des membres inférieurs.

Il est à noter que dans les situations B et D un maintien correct de la tête dans la position imposée est indispensable pour l obtention d une réponse caractéristique

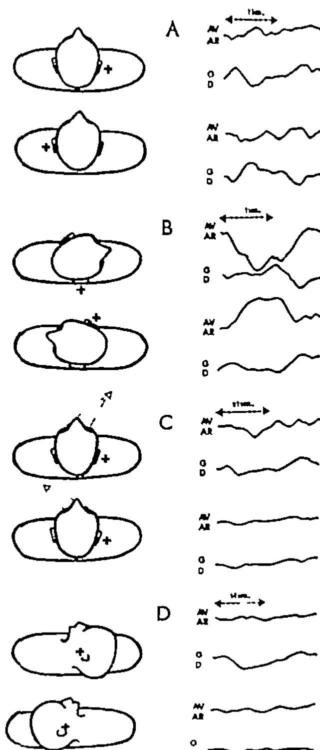


Fig 1 Etude statokinésimétrique des déplacements du centre de gravité du corps d'un sujet recevant une stimulation galvanique labyrinthique de 0,5 mA pendant 4 secondes. (A) Stimulation seule; (B) stimulation rotation de la tête; (C) stimulation rotation des yeux, (D) stimulation *inclinaison de la tête.*

II *Etude du réflexe H et T*

De nos résultats préliminaires il ressort que les *réflexes* H et T varient d amplitude en sens in verse suivant les variations de tonus des muscles nucaux et des muscles oculaires. Cette variation est asymétrique entre la jambe droite et la jambe gauche (Fig. 2).

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TISSUE CULTURE OF THE ORGAN OF CORTI AND THE ISOLATED HAIR CELLS FROM THE NEWBORN GUINEA PIG

T. Yamashita and K. H. Vosteen

From the E.N.T. Department, University of Frankfurt am Main, BRD

Abstract. The organ of Corti and isolated hair cells from newborn guinea pig were cultured with the Rose chamber method. The hair cells could be maintained for more than 20 days after explantation when the organ of Corti was cultured as a whole, though the isolated hair cells swelled and degenerated within about 13 hours after explantation. By comparison between the tissue culture of the hair cells with the organ of Corti and isolated hair cell culture, the following conclusions were reached. (1) There are some functional correlations concerning the nutritional requirements and cell metabolism between the hair cells and the supporting cells in addition to the structural correlations. (2) There are no distinct fundamental differences between both inner and outer hair cells about their affectability as a single cell level.

Many investigations have been carried out in making clear the structures and functions of the inner ear. The first attempts have been done by morphological ways with the fixation and staining. Later the histochemical and electrophysiological approaches have played a great role to know the function of the inner ear. The application of electron-microscopical techniques have contributed considerably to our knowledge of the cytology of the inner ear. But the observations of the inner ear cells grown in tissue culture with phase-contrast microscopy might be also important from now on, because of dealing with real living cells without any fixation and staining.

The first successful attempt in cultivating the inner ear cells in vitro has been done by Fell (1938) using the chick embryo otocyst. Since Fell's report, many investigations have communicated various techniques for the in vitro development of the otocyst, but most of them have been done using the fowl embryo otocyst (Friedmann, 1956, 1959, 1961, 1968, 1969; Friedmann & Bird, 1961, 1967; Reinecke et al., 1960; McAlpine & Friedmann, 1963; Shambaugh & Orr, 1963; Iwai, 1964; Orr, 1965, 1968; Kitano, 1968). Some works have been done with the mammalian otocyst (Maximow, 1925; Lawrence & Merchant, 1953; Sugawara, 1964; Van De Water & Ruben, 1971, 1973*a*; Van De Water et al., 1973*b*).

Owing to the special structure of the inner ear it is better to choose the material that is already well differentiated. There are few informations defining the in vitro development of the well differentiated mammalian inner ear. Shambaugh (1956) and Sugawara (1964) have investigated the in vitro development of Corti's organ of newborn cat. Iwai (1959) reported the in vitro development of the spiral ganglion of newborn rabbit. Recently Iwai et al. (1967) and Okano et al. (1971) showed some observations of the inner ear cells from newborn dog by tissue culture technique. There have been no report of any cultivation of the inner ear of newborn guinea pig in vitro.

The organ of Corti and isolated hair cells of the inner ear of newborn guinea pig have been cultivated in Rose chambers forming the explant to grow in a thin flat layer suitable for phase-contrast microscopy.

MATERIAL AND METHODS

The experiments were carried out on 60 newborn guinea pigs only 1 and 2 days old. The animals were decapitated, the whole temporal bone was quickly dissected out of the skull using sterile technique, the bony wall of the cochlea was chipped away and the apical part of the membranous cochlear duct was removed from

directe sur le motoneurone α facilitatrice et sur la boucle γ inhibitrice au niveau médullaire ou vice versa.

Nous avons tenu a attirer l attention sur l im portance des voies fonctionnelles vestibulo-oculo-nucales dans l activité tonique posturale orthostatique en insistant tout particulièrement sur ces deux dernières par le rôle qu elles jouent dans l équilibre. On ne doit pas négliger d exa miner leur fonctionnement au cours de certains déséquilibres dont l étiologie vestibulaire n est pas en cause et ce sera tout particulièrement le cas au cours de certains déséquilibres inexpliqués du syndrome subjectif post-commotionnel des traumatisés crâniens et au cours de certaines intoxications. L étiologie tronculaire du déséqui libre intéressant les noyaux du III du IV du VI du XI et le noyau supraspinal devra être envisagée en l absence de localisation cérébrale ou cérébelleuse.

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Tirés à part

J B Baron M D
Laboratoire de Statokinésimétrie
Centre psychiatrique Sainte-Anne
1 Rue Cabanis-75014 Paris
France



Fig. 2. Macrophages from the explant of the organ of Corti. Scale = 30 μm (a 7-day culture).

sessed one oval nucleus with several nucleoli and they had many granular materials of active motility in cytoplasm.

The outgrowth of fibroblasts from the explant of CORTI began within 1 day after explantation (DAE) and reached its peak on about 15 DAE, covering almost the whole surface of the cover glass. During 30 DAE, fibroblasts aggregated in groups and finally made several degenerating tissue mass on more than 40 DAE. Most of fibroblasts were thought to grow out from the layer of the thin endothelium of the basilar membrane, which was faced with the scala tympani and was of mesenchymal origin (Fig. 1).

(b) *Macrophages.* After 6 to 8 DAE, the isolated wandering cells of fair motility appeared in the sheets of outgrow epithelial cells or the outgrow fibroblasts layers from the explant of Corti, were highly amoeboid and could be seen to be phagocytic. They were so-called macrophages which were mostly round and spindle in shape, were mononucleate and had many granular materials and vacuoles various in size in the cytoplasm. They also had a transparent hyaline membrane which extended towards the outside of the cells (Fig. 2).

2. *Epithelial cells*

From 2 to 4 DAE, epithelial cells emerged as sheets of cells closely adherent to each other from the explant of CORTI and these outgrowths mainly came from the supporting cells, especially the Hensen's cells and cells of Claudius. The sheet of epithelial cells took place connecting to the outer margin of the explant, and on the outmost area of this sheet the fibroblasts layer grew extensively (Fig. 3).

In this period, the cytological characteristics of the epithelial cells appeared as polygon in shape, and showed one round nucleus with several small nucleoli at the periphery and a number of granular materials in the cytoplasm.

Generally speaking, *in the first stage, it is* possible to decide the origin of the outgrow epithelial cells, because the cells which emerge from the various tissues in fresh culture become altered as compared with their counterparts in the original tissue, and a little consideration of the normal histology of the various tissues of the body leads to the conclusion that the tissues of each organ differ morphologically much more in the arrangement of their cells than they do in the actual cell-type which they contain. In fact, also in this experiment, by daily observation on morphological specificity of each cells and cell arrangement, it was possible *to distinguish the* outgrow epithelial cells from Hensen's cells (*Fig. 4a*) and Claudius cells (*Fig. 4b*) only in the first stage, because the fresh outgrow epithelial cells from Hensen's cells contained a few



Fig 1 Fibroblasts (*F*) from the layer of thin epithelium of basilar membrane (*EB*). The outgrow *epithelial cells sheet* (*E*). Original Hensen s cells (*H*). Scale in *a* = 50 μm. Scale in *b* = 30 μm (a 3-day culture).

the bony cochlea under the dissecting microscope For the tissue culture of the organ of Corti as a whole the organ of Corti with basilar membrane (CORTI) was separated from the membranous cochlear duct For the isolated hair cell culture the hair cell layers were again separated from another part of the organ of Corti with a fine scalpel and forceps.

The Rose chamber (Rose, 1958) was used which was formed of 2 large cover glasses, separated by a rubber gasket and held together by 2 metal plates and 4 screws. The explants were put on a cover glass and covered by a cellophane dialysis strip and the parts of the chamber were assembled. Nutrient fluid was then injected through the rubber gasket.

The following nutrient fluids were used in this study Medium A 50% human ascitis fluid 50% Gey s balanced salt solution 100 u/cc penicillin and 0 1 % phenol red as a pH indicator Medium B 85 % nutrient mixture F 10 (GIBCO*), 12.5% horse serum 2.5 fetal calf serum 100 u/cc penicillin and 0 1 % phenol red. Both media showed encouraging results for the growth of the cells, but there was a slight difference between them medium B was better for the developing epithelial cells and medium A for mesenchymal cells. The nutrient fluid was changed as needed according to the pH indicator usually once every 4 days. The cultures were incubated at a temperature of approximately 37°C. Daily observations were made and photographed under a phase-contrast microscope

RESULTS

I *Tissue Culture of the Organ of Corti as a Whole*

1 *Mesenchymal cells*

(*a*) *Fibroblasts* Fibroblasts emerged as a loose network of cell from various sources of explant, all of which were however mesenchymal They showed spindle, polygonal or oblong cell bodys with the spindle-shaped process. Each cell pos

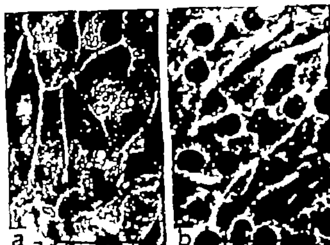


Fig. 4. Fresh outgrow epithelial cells from the Hensen cells (*a*) contain several lipid-like granules in the cytoplasm, and they appear a little longer in shape than the cells from the Claudius' cells (*b*). Scale = 30 μm (a 3-day culture).



Fig. 5. Normal outgrow of epithelial cells. Scale = 30 μm (a 5-day culture).

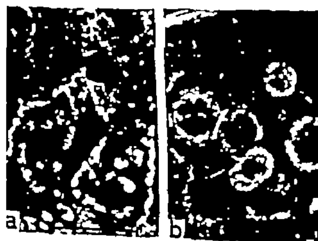


Fig. 6. Degenerating pattern of the outgrow epithelial cells. Scale = 30 μm (a 15-day culture).

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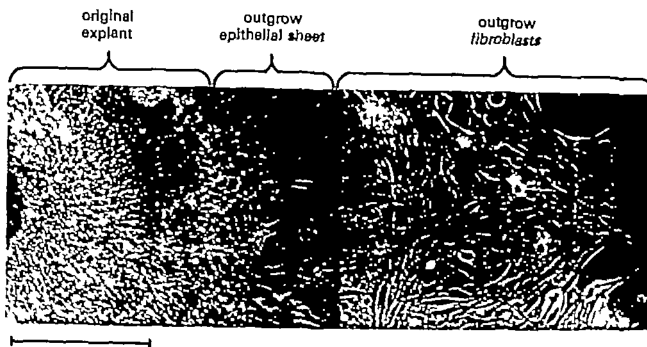


Fig 3 Typical figure of the cultivated explant of the organ of Corti. Scale = 200 μm (a 3-day culture).

lipid granules in the cytoplasm and were a little longer in shape than the cells from Claudius cells.

The alterations, however appeared to occur in steps, the cell form was gradually enlarged and the granular materials began to have movement which was not so active as in the case of fibroblasts (Fig. 5). In this period, it became impossible to distinguish between two of them

Within 6 to 7 DAE, the formation of sheets of these outgrow epithelial cells reached its peak and they were maintained their "healthy condition till about 15 DAE and later many small (Fig. 6*a*) or a single large vesicle (Fig 6*b*) appeared in the cytoplasm as the process of degeneration

During 5 to 7 DAE, several hair cells were found in these epithelial cell sheets in some cases of explants (Fig. 7). These hair cells were isolated from one another and did not form groups, and they were identified from another epithelial cells because of having the auditory hair as a morphological characteristic and being oval in shape. Through daily and detailed observations, it was noticed that the maintained original hair cells seemed pushed aside by new outgrow epithelial cells and finally isolated as foreign bodies" in the sheets of epithelial cells, and therefore it could be said that these hair cells observed in the culture should never be the outgrow cells developing from the hair cell origin Even if the new epithelial cells could emerge from the hair cell origin in this experiment it was impossible to identify them morphologically under a phase-contrast microscope.

3 The hair cells within the explant area

Within the explant area, as early as 3 hours after explantation (HAE), both inner and outer hair cells began to swell more or less. Most of them reached their peak of swelling on about 12 to 15 HAE (Fig. 8) and returned to the normal form completely or incompletely within 3 DAE (Fig. 9), but some of them degenerated and did not recover During these changes, the outer hair cells swelled more severely lost the arrangement more easily and were less successful to recover than the inner

After 3 DAE, the pattern of changes of the hair cells depended upon whether the hair cells



Fig. 10. Well arranged and maintained outer hair cells covered by the tectorial membrane. Scale = 30μm (a 20-day culture).

were covered with the tectorial membrane or not. The hair cells which were covered with the tectorial membrane had great resistence against degeneration and they remained unchanged or almost in original form for about 20 DAE (Fig. 10). The hair cells which were not covered with the tectorial membrane appeared disordered in arrangement, but some of them were maintained with the auditory hair for 15 DAE, though they showed half swelling in appearance (Fig. 11).

II. *Isolated Hair Cell Culture*

When the organ of Corti was cultured as a whole, it was difficult to observe the hair cells as a total figure because of the special three-dimensional structure of the organ of Corti.

By separating the layers of Hensen's cells which were easily distinguished for containing the lipid granules in the cytoplasm from the membranous cochlear duct, the single hair cell layer or single hair cells could be easily obtained with Hensen's cell layer together from another part of the organ of Corti. These single hair cell or single hair cells which were in contact with the Hensen's cell layer were cultured in the similar manner as normal tissue culture and observed in time-lapse under a phase-contrast microscope.

The single hair cell layer or single hair cells

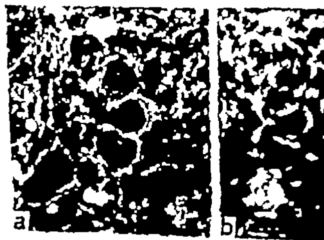


Fig. 11. Half-swollen and disarranged outer hair cells without the tectorial membrane (*a*). The auditory hair (arrows) can be seen at correct focus (*b*). Scale = 30 μm (15-day culture).



Fig 7 Original hair cells (arrows) in the outgrow epithelial cell sheet. Scale = 30 µm (a 6-day culture).



Fig 8. Swollen hair cells at an early stage after cultivation. Scale = 30 µm (a 15-hour culture).



Fig 9 Recovered inner hair cells after swelling. Scale = 30 µm (a 3-day culture).



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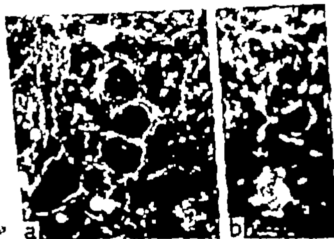


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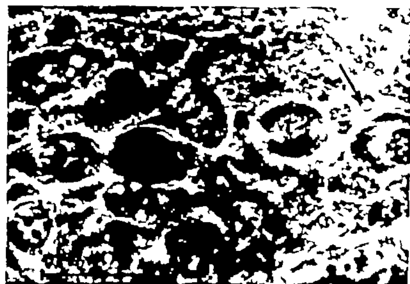


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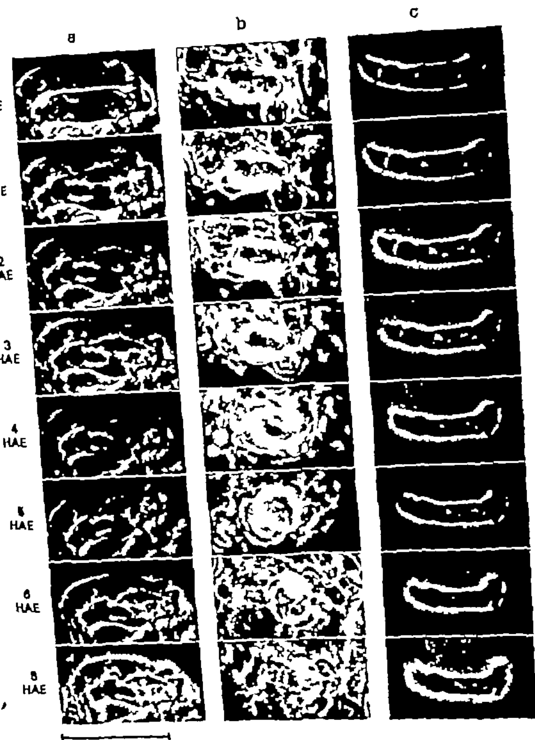


Fig. 13. Time-lapse changes in the isolated hair cell culture. (a) Swelling type of the outer hair cell (non-t) pedal pattern); (b) Swelling type of the inner hair cell. (c) atrophy type of the outer hair cell. MAE represents time in minutes after explantation. HAE represents time in hour after explantation. Scale 50 μm.

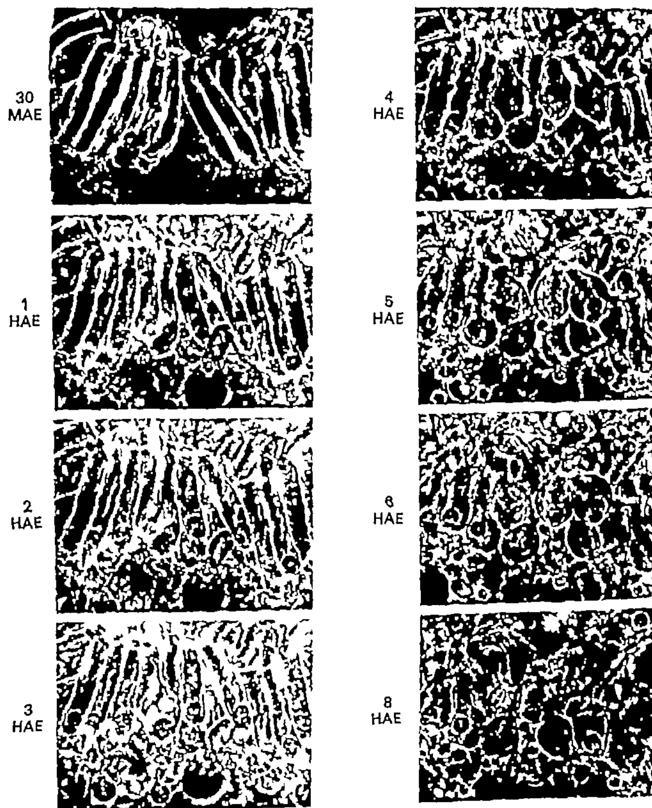


Fig 12 Time-lapse changes in swelling type of the isolated outer hair cell culture. Ruptured hair cells (arrows) can also be observed in 8 HAE. MAE represents time in minutes after explantation. HAE represents time in hours after explantation. Scale 50 μm.

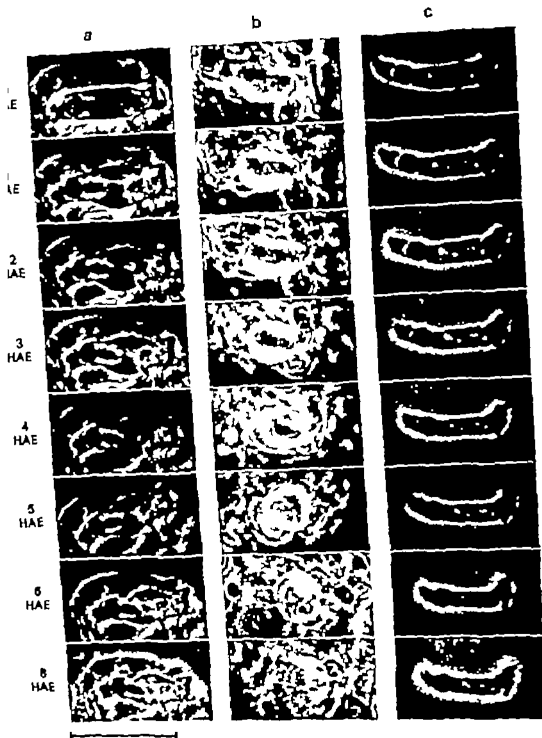


Fig. 1 Time-lapse changes in the isolated hair cell culture. (*a*) Swelling type of the outer hair cell (non-typical pattern); *b* swelling type of the inner hair cell, (*c*) atrophy type of the outer hair cell. MAE represents time in minutes after explantation. HAE represents time in hour after explantation. Scale 50 µm.

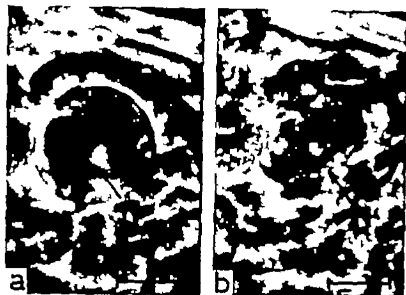


Fig 14 Nucleus of the inner hair cell (*a*) swells and its diameter increases after rupture of the cell body (*b*). *N* nucleus. Scale = 10 μm (an 8-hour isolated hair cells culture).

degenerated very quickly in vitro and could be classified roughly into 2 types by the changing of the cell body the swelling type and the atrophy type

(a) Swelling type

Just after explantation, the outer hair cells were cylindrical in shape with a round base On the apical surface they carried an annular reticular lamina with auditory hair The nucleus which was round in shape and had small nucleoli at the periphery was situated closer to the basal pole of the cell. The cytoplasm had granular materials especially in the apical and the basal part.

The inner hair cells were also cylindrical in shape but the length was shorter and the width was wider than the outer hair cells just after explantation The cytoplasm had much granular materials on an average The nucleus the reticular lamina and the auditory hair were just like those of the outer hair cells

The cytoplasm and the nucleus of both inner and outer hair cells of this type showed no staining by Erythrocin B (Phillips, 1959) So the cell and cell membrane were thought to be "living" and healthy

The granular materials in the cytoplasm had no movement till the cell ruptured.

In most cases of the outer hair cells, from 1 or 2 HAE, the cell body began to swell in the basal part. On 5 to 6 HAE, the swelling was at the peak and the cell body became nearly perfectly round without the part of the reticular lamina On more than 8 to 10 HAE, the cell ruptured and took way to atrophy (Fig 12)

In some cases of the outer hair cells, the swelling began from the middle part of the cell body and the atrophy came gradually before the swelling had reached its peak (Fig. 13*a*).

In all cases of the inner hair cells, the swelling began from 1 HAE, reached its peak within 5 to 6 HAE and the rupture and atrophy came later (Fig. 13*b*).

About both hair cells, till the rupture of the cells, the nuclei had such a slight change that small vesicles appeared at the periphery of nuclei but after the rupture the nuclei themselves also swelled and increased the diameter especially in the inner hair cells (Fig. 14). The reticular lamina and the auditory hair showed no changes after the rupture of the cell.

(b) Atrophy type

Just after explantation the cell membrane of the outer hair cells of this type showed a little atonic in the basal part which had been in contact with the cells of Deiters

In the cytoplasm the granular materials which were thought to be mitochondria and lysosomes had very rapid movement, that might be so-called "Brownian movement"



Fig. 15. Outgrow epithelial cells from the isolated Hensen's cells. Scale = 30 μm (a 5-day culture).

The cytoplasm and nucleus were well stained by Erythrocin B. So these cells were thought to have already some changes in the cell membrane by mechanical damages during the cultivating procedure.

With the lapse of time, the cells of this type gradually became atrophic, the granular materials tended to increase in number and small or large vesicles appeared in the cytoplasm. Within 13 HAE, the "Brownian movement" stopped and the cell became smaller in shape (Fig. 13c).

About the Hensen's cells, after 3 to 4 DAE, the new epithelial cells came out of the separated Hensen's cell layer and were maintained for more than 3 weeks in vitro (Fig. 15).

It must be mentioned that the isolated single hair cell layer or single hair cells degenerated almost perfectly only within 13 HAE, though the separated Hensen's cell layer which was explanted at the same time with the hair cells developed and was maintained for 3 weeks.

DISCUSSION

In this experiment the hair cells were maintained *in vitro* for more than 20 DAE, but the outgrowth of the epithelial cells from the hair cell origin could not be identified, though the outgrowth of the epithelial cells from the supporting cells of the organ of Corti were extensive. In some cases, the hair cells were found in the sheets of outgrow epithelial cells on 6 to 7 DAE, maintained for about 2 days and later degenerated. So these hair cells must be the original ones themselves and not the now *outgrew* epithelial cells from the hair cell origin. Though Sugawara (1964) reported the outgrowth of the epithelial cells from the hair cell origin using newborn cat, Shambough failed to distinguish exactly the outgrow epithelial cells from the inner ear of newborn cat from another epithelial structure, such as skin, respiratory mucosa or gastro-intestinal mucosa (Reinecke et al., 1960). Iwai et al. (1967) also reported using newborn dog that the hair cells did not develop, though they were maintained for 2 weeks. So it may be possible to say that the well differentiated hair cells as in case of nervous cells cannot develop any more in vitro, in contrast with the supporting cells.

Within the explant area, the hair cells showed the morphological degenerative changes such as swelling at an early stage of culture, but after several days some of them recovered almost perfectly especially in the inner hair cells. Several electrophysiological investigations (Wever et al., 1949. Perlman & Kimura, 1959. Konishi et al., 1961) showed that the functions of the hair cells which had once come down by anoxia could recover when oxygen was supplied again. Yamashita et al. (1973) also reported the similar findings with the histochemical approach. Iwai

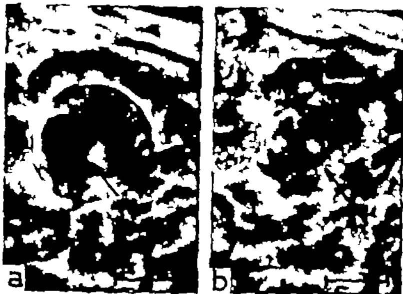


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ments were observed in the cytoplasm of the hair cells when they were intact and actively living. However the extensive granular movements like *Brownian movement* appeared when the cell membrane of the hair cells was already damaged more or less such as in the atrophy mentioned above or the swelling type at the maximal swelling. The following can be thought. Originally the cytoplasm of the hair cells is so-called "gel" condition and it has no granular movement. By the change of the permeability of membrane according to the damage of cells, the cytoplasm changes from "gel" to "sol" and the unphysiological granular movement like "Brownian movement" appears. So, in other words, it can be said that the granular movements in the cytoplasm is a sign of the membrane damage in case of the hair cells.

In this experiment, the outer hair cells were easily affected by the changes of circumstances in culture than the inner when the organ of Corti cultivated as a whole. Much greater differences are found in the behavior pattern of both hair cells in other experimental conditions. Davis (1953) found that the outer hair cells were more easily injured than the inner by sounds of considerable strength. Hawkins & Lurie (1962) showed that the inner hair cells suffered injury after administration of streptomycin. Nevertheless, the outer hair cells are always more sensitive to drugs than the inner (Ward & Fernandez, 1961 Beck & Krahl, 1962, Engström & Kohonen, 1965). They are also easily damaged by circulatory arrest (Kimura & Perlman, 1956) and anoxia (Yamashita & al., 1973). On the contrary when the isolated hair cells were cultivated, both hair cells had not any great differences in their behavior pattern. In the present experiment, both inner and outer hair cells swelled and degenerated similarly. From these findings, the differences in the behavior pattern of both hair cells mentioned above are thought to depend on each different standpoint in the structure of the organ of Corti which, for example, the outer hair cells are surrounded at the sides largely by intercellular fluid in contrast to the inner (Guild, 1932). Though electron-microscopical and histochemical investigations offer some informations about the dissimilar structural differentiation of these cells (Engström & Wersäll, 1958 Iurato 1961), it can be said that at a single cell level there are no fundamental differences between both hair cells about their affectability at least in vitro.

ZUSAMMENFASSUNG

Gewebekulturen von Haarzellen lassen sich entweder durch Inkubation des gesamten Cortischen Organes oder durch Züchtung isolierter Haarzellen gewinnen.

Bei Explantation des gesamten Cortiorganes beträgt die Überlebenszeit der Haarzellen mehr als 20 Tage, jedoch ist eine laufende Beobachtung des Aussehens der Epithelzellen dabei nicht möglich. Bei Kulturen von isolierten Haarzellen kommt es schon innerhalb von 13 Stunden zur Degeneration und zur Schwellung der Zellen.

Durch Vergleich von gezüchteten Haarzellen aus dem gesamten Cortischen Organ einerseits und von Kulturen isolierter Haarzellen andererseits kommen wir zu folgenden Schlußfolgerungen 1) Für die Ernährung und den Stoffwechsel der Haarzellen ist die intakte Struktur der Stützzellen erforderlich. 2) Bei Kulturen von isolierten Sinneszellen unterscheiden sich innere und äußere Haarzellen nicht in ihrer Empfindlichkeit gegen Zellschädigungen.

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(1964) showed morphologically in vitro the recovery of the nervous tissue which had once degenerating process. The investigations about the recovery of once damaged hair cells are of interest for the therapy of the inner ear pathology Furthermore it is also important to know whether a complete recovery is possible and to what extent of damage would interfere with a reasonable recovery However the present observation did not provide enough information of these things.

For long time there have been many discussions about the correlation between the tectorial membrane and the auditory hair of the hair cells The present data showed that the hair cells covered with the tectorial membrane could be maintained for longer time than those not covered with it in the explant area It may be said that the tectorial membrane contributes to the maintenance of the hair cells to some extent

In tissue culture of the organ of Corti, the hair cells which were supported by many kinds of supporting cells were maintained for more than 20 DAE. On the contrary in the isolated hair cell culture the single hair cell layer or single hair cells which were separated from its supporting cells degenerated in short time. Most simple reasons for these findings might be the followings (1) the hair cells which are separated from their supporting cells are easily damaged mechanically during the procedure of cultivation especially by the pressure of the cellophane strip (2) generally in tissue culture the duration of survival depends greatly on the size of the tissue explanted Larger pieces of tissue tend to survive better than smaller ones and smaller pieces of tissue are again usually more viable than isolated cells. It is possible that in general, the isolated hair cells may be difficult to be maintained in vitro But the isolated Hensen's cells can survive and grow Therefore the isolated hair cells may have some weakness of their own In case of the hair cells of the atrophy type in this experiment, it can be explained by the reason of (1) for their membrane was damaged, as was detected by the Erythrocin B staining. However the swelling type of them is difficult to be explained by only the reason of (1), because the membrane was intact in outline, and even in case that a single hair cell was perfectly protected from the direct pressure of the cellophane strip in the ample space beside large tissue masses, the hair cell swelled and degenerated easily And so it follows necessarily that these findings mentioned above can not be explained by only the reasons of (1) and (2), it should be discussed on the standpoint of the correlation between the hair cells and the supporting cells Originally the inner and outer hair cells are connected with the supporting cells the inner limiting cells, the inner phalanges, the inner and outer rods, Deiter's cells, Hensen's cells and cells of Claudius It is easy to consider that the hair cells are mechanically protected by the supporting cells from any kinds of damages in addition to supporting the structure Besides, from the present data, it may be possible to say that the hair cells and the supporting cells have some functional connections concerning the nutritional requirement and cell metabolism

In case of the isolated hair cell culture, the reticular lamina and the auditory hair showed no changes under phase-contrast microscopical observation during the short time after explantation when the hair cell himself had swollen, ruptured and degenerated Also in case of the culture of the organ of Corti as a whole no irregularity was noticed in the reticular framework for about 1 to 2 DAE when most of the hair cells swelled more or less. Up to now many investigators have chosen the reticular framework as the degenerating sign of the hair cells by phase-contrast microscopical observations. This is correct only in case of chronic changes of the hair cells And so it is necessary to pay attention when the acute change of the hair cells is observed

The granular materials in the cytoplasm had some active movement in the fibroblast and the outgrow epithelial cell These movements depend on the physiological flow of the cytoplasm and it might be considered as a sign of "living" for these cells. On the other hand, no granular move-

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(1964) showed morphologically in vitro the recovery of the nervous tissue which had once degenerating process The investigations about the recovery of once damaged hair cells are of interest for the therapy of the inner ear pathology Furthermore it is also important to know whether a complete recovery is possible and to what extent of damage would interfere with a reasonable recovery However the present observation did not provide enough information of these things.

For long time there have been many discussions about the correlation between the tectorial membrane and the auditory hair of the hair cells. The present data showed that the hair cells covered with the tectorial membrane could be maintained for longer time than those not covered with it in the explant area. It may be said that the tectorial membrane contributes to the maintenance of the hair cells to some extent.

In tissue culture of the organ of Corti, the hair cells which were supported by many kinds of supporting cells were maintained for more than 20 DAE. On the contrary in the isolated hair cell culture, the single hair cell layer or single hair cells which were separated from its supporting cells degenerated in short time. Most simple reasons for these findings might be the followings (1) the hair cells which are separated from their supporting cells are easily damaged mechanically during the procedure of cultivation especially by the pressure of the cellophane strip (2) generally in tissue culture the duration of survival depends greatly on the size of the tissue explanted Larger pieces of tissue tend to survive better than smaller ones and smaller pieces of tissue are again usually more viable than isolated cells. It is possible that in general the isolated hair cells may be difficult to be maintained in vitro But the isolated Hensen's cells can survive and grow Therefore the isolated hair cells may have some weakness of their own In case of the hair cells of the atrophy type in this experiment it can be explained by the reason of (1) for their membrane was damaged, as was detected by the Erythrocin B staining. However the swelling type of them is difficult to be explained by only the reason of (1) because the membrane was intact in outline and even in case that a single hair cell was perfectly protected from the direct pressure of the cellophane strip in the ample space beside large tissue masses the hair cell swelled and degenerated easily And so it follows necessarily that these findings mentioned above can not be explained by only the reasons of (1) and (2) it should be discussed on the standpoint of the correlation between the hair cells and the supporting cells. Originally the inner and outer hair cells are connected with the supporting cells the inner limiting cells, the inner phalanges, the inner and outer rods, De ter s cells, Hensen s cells and cells of Claudius It is easy to consider that the hair cells are mechanically protected by the supporting cells from any kinds of damages in addition to supporting the structure. Besides, from the present data, it may be possible to say that the hair cells and the supporting cells have some functional connections concerning the nutritional requirement and cell metabolism

In case of the isolated hair cell culture, the reticular lamina and the auditory hair showed no changes under phase-contrast microscopical observation during the short time after explantation when the hair cell himself had swollen ruptured and degenerated Also in case of the culture of the organ of Corti as a whole no irregularity was noticed in the reticular framework for about 1 to 2 DAE when most of the hair cells swelled more or less. Up to now many investigators have chosen the reticular framework as the degenerating sign of the hair cells by phase-contrast microscopical observations This is correct only in case of chronic changes of the hair cells. And so it is necessary to pay attention when the acute change of the hair cells is observed.

The granular materials in the cytoplasm had some active movement in the fibroblast and the outgrow epithelial cell. These movements depend on the physiological flow of the cytoplasm and it might be considered as a sign of "living" for these cells. On the other hand, no granular move-

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Makoto Igarashi and Yubo Kato[1]

From Baylor College of Medicine Houston, Texas, USA

Abstract By utilizing the squirrel monkey rail test, postoperative compensation status after unilateral saccular macula destruction, unilateral utricular nerve section and unilateral lateral ampullary nerve section, were studied in a quantitative fashion and the results were statistically compared. First, it was confirmed that the preoperative random assignments of subjects were evenly distributed among different experimental categories and therefore inter-categoric statistical comparisons of postoperative status were valid. Minimal effect after the unilateral saccular macula ablation toward the maintenance of body equilibrium was reconfirmed. The utricular input is probably the most important for the maintenance of body equilibrium function, inasmuch as slightly less equilibrium disturbance was found after unilateral lateral ampullary nerve cut even though the difference was not significant.

After partial ablation of the peripheral labyrinthine end organ, the condition of body dysequilibrium changes dynamically. Thus, it is important to study the body equilibrium function along the time course which represents systemic imbalance and eventual compensation from disturbances occurring within the system. Thus, any investigation of equilibrium function conducted only at one fixed time has only limited merit.

Quantitative comparisons of the compensation of the body equilibrium function along the time span will demonstrate the relative importance of the different parts of the vestibular end organ system in locomotive body equilibrium function and recovery from injury or loss of part of the system. Histological confirmation should be performed in all experimental and sham subjects in order to correlate the extent of ablation to the disturbances in performances and to recovery. The importance of this morphological confirmation has been recognized in the past especially after surgically created lesions.

By utilizing partial ablation procedure in different experimental animal species, the contribution from the different vestibular end organs to body equilibrium function has been investigated by Versteegh (1927), and McNally & Tait (1933), McNally & Stuart (1942), Jongkees & Philipszoon (1964), Mair & Fernandez (1966), Igarashi (1968, 1970), Igarashi et al. (1970), Igarashi & Miyata (1972), Igarashi et al. (1972) and others.

The purpose of the present communication is to demonstrate the difference in the effect after selective unilateral retrenchment of macula sacculi, maculi utriculi, or lateral ampullary nerve in the squirrel monkey. Inter-categorical comparisons were performed statistically.

METHOD AND PROCEDURE

Subjects

The subjects used in the present experimental series were South American squirrel monkeys (Saimiri sciureus). Originally they were from Colombia and quarantined in the Miami Florida area before being sent to our vivarium in Houston, Texas. They were healthy young adults, about two years old, and with no preference as to their sex. Their body weights ranged from 550 to 700 grams. The acquisition of these

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Reprint request to
T Yamashita M D
ENT Department of
Kansai Medical University
1 Fumi ono-cho
Moriguchi shi Osaka 570,
Japan

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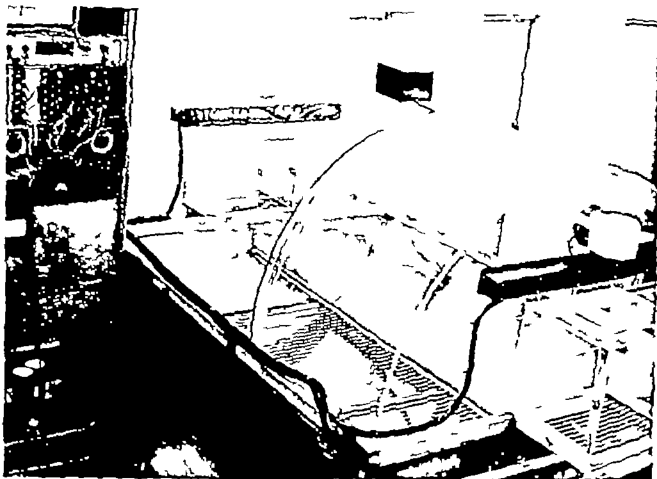


Fig 1 Bird's eye view of the squirrel monkey rail test device. Descriptions in the text.

experimental subjects was made at many different times over several years and therefore, the subjects belonged to randomly different original batches. The animals were acclimated to be fed Purina Monkey Chow some fruits, and water which contained vitamin complex. A pair of animals were housed in a 75 cm cubicle metal cage with ordinary room lighting and air ventilation. Room temperature was maintained at 76 to 80°F with desirable humidity

Apparatus

The rail test apparatus which was described by Igarashi in 1968 consists of a shuttle avoidance situation with a rotating rail positioned between the two shuttle end compartments (Fig. 1). The rail is cross-sectionally X-shaped (3 8 cm × 3 8 cm), and the entire length is 180 cm. This rail can be rotated along its longitudinal axis at a speed up to 1000 rpm without any danger. The rotating rail is centered in a cylindrical enclosure, which is 180 cm in length and 150 cm in diameter (positioned horizontally). The rotating rail is positioned parallel to the longitudinal axis of the cylinder

The shuttle compartments (30 cm × 30 cm 40 cm) of plexiglass are stationarily mounted to th end of the cylinder so that the subject can proceed from one shuttle end box, across the rail to the opposite shuttle end box

During the training and testing procedure the entire apparatus is covered with a heavy black velvet cloth, with small peep holes. The conditioned stimulus (CS) is the darkening of an incandescent bulb o er the occupied shuttle compartment and the simultaneous illumination of an identical light over the unoccupied box. The unconditioned stimulus (UCS) is a scrambled manually viable intensity electric shock produced by a Foringer 1154-M11 shock power

supply and fed through a Foringer 1925 grid shock scrambler to 6 mm diameter stainless steel bars which comprise the floor of the shuttle compartment, and also underlie the rotating rail. The rail is not electrified but can be rotated continuously so that it is impossible for the subject to remain on it. The CS-UCS interval is two seconds (timed by a Lehigh 1309 timer), and the intertrial interval is 20 seconds (timed by a Grason–Stadler E4300 timer).

Both the CS and the UCS are continuous after presentation. Two Foringer 1186-M1 sequence coordinators are used to switch the light and electric shock between the two shuttle compartments.

Screening and training

Squirrel monkeys were screened to eliminate unsuitable subjects for this conditioning experiment, such as those which responded improperly to the rail test apparatus. These include continuous random activity freezing to electrified grids, etc. Ample time was given to let naive subjects explore the entire apparatus before starting the screening procedure. During this screening maneuver stimulus presentation was manually controlled. The rail speed was manually adjusted for each subject (usually below 90 rpm) according to its behavior and ability to maintain equilibrium function. Usually 30–60 trials (CS-UCS presentations) were given in a single block.

The basic training period consisted of the presentation of about six blocks of about 60 trials each, so that the avoidance rail-running response would become reflexive. Subjects simultaneously received conditioning and physical practice at low speed (200 rpm) rail running. When a subject fell or jumped off the rail, the rail was stopped in order to let the subject climb back onto it.

Pre-operative threshold measurement

This stage is concerned with determining the highest speed of rail rotation at which the subject could no longer traverse the rail without falling off. The present rail test device can provide the maximum of 1000 rpm speed without any danger to either the subject or the examiner.

Initially the rail rotating speed was set at 0 rpm. If the subject successfully crossed it, the speed was increased in increments of 50 rpm after each successful traversing until the speed of 1000 rpm was reached, or until the subject made four consecutive unsuccessful attempts of traversing the rail at any certain given rpm. This rpm value was defined as the subject's "threshold of dysequilibrium". When the subject fell, the rail was immediately stopped in order to let him climb back up on it, and subsequently reach the safe shuttle box. Usually the CS-UCS interval was 2 seconds and the intertrial interval remained at 20 seconds during this test procedure. No signs of fatigue were found even after testing at high rpm levels.

Surgery

Experimental categories in the present series are saccular macula destruction (S), utricular nerve section (U), and lateral ampullary nerve section (L). All surgical procedures were performed unilaterally under aseptic conditions. Intraperitoneal injection of sodium pentobarbital (30 mg/kg) was used for general anesthesia. A retroauricular atticotomy approach was used and the major part of the surgery was performed under the operating microscope. After retracting the external acoustic meatus skin and tympanic membrane anteriorly the postero-superior edge of the bony external meatus wall was partly removed by a small angled curette. The incus was removed after subluxating the incudostapedial articulation with a fine pick. The stapedial tendon was divided and the annular ligament of the stapes was separated all around the stapedial base by a very fine pick. Attempts were made to remove the stapes in toto however some were removed in a piecemeal fashion. Intense movement of perilymph was strictly avoided during this procedure. The anterior inferior edge of the vestibular fenestra was drilled off very little to acquire a better view of the entire saccular macula. The saccular membrane was ruptured and a fine pick was inserted to

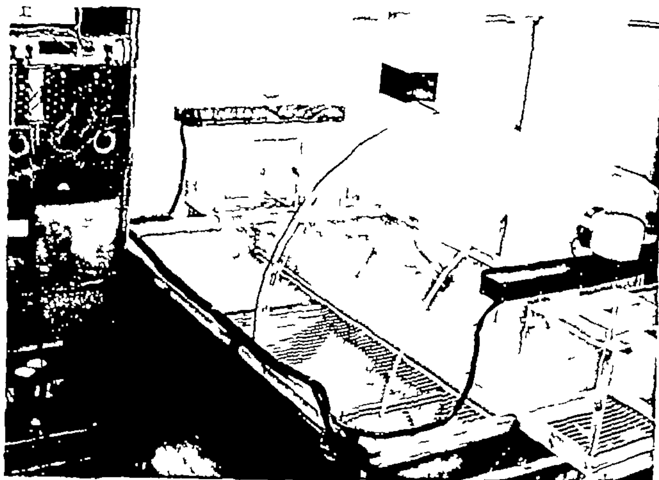


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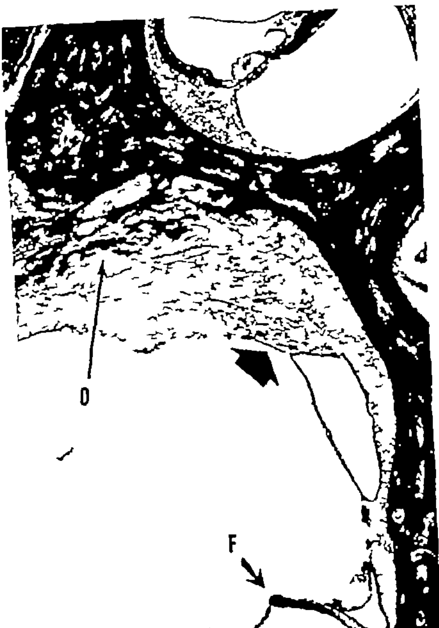


Fig. 2. Photomicrograph demonstrates horizontal-sectional view of the five day postablative condition of the area of the macula sacculi in squirrel monkey. Notice the saccular space is almost occupied by the connective tissue (large arrow). Some ossification (*O*) can be noticed already. Also tight closure of the utriculo-endolymphatic fold (*F*) can be seen. H & E staining. 97

indicated that these means were not significantly different, $F (2, 18) < 1$. It was thus confirmed that randomly assigned squirrel monkeys were evenly distributed *among different experimental* categories as far as the equilibrium function is concerned. Therefore, the postoperative inter categoric data analysis could be assumed to relate observations of comparably treated subjects.

The number of calendar and trial days each

destroy the saccular macula. The rupture and dislodgement of the statoconia had to be ensured during this procedure so that the saccular macula carried no more gravito-inertial receptor function The use of aspiration was minimized during this entire procedure except for removing bone dust and blood Thereafter the vestibular fenestra was sealed by autogenous adipose graft which was kept in place by gelfoam in the tympanic cavity Seven squirrel monkeys belonged to this category

For the group of unilateral utricular nerve section the antero-superior edge of the vestibular fenestra was very slightly drilled off after the stapes was removed, in order to obtain a better visualization of the utricular macula and nerve An extremely fine and sharp pick was used to section the utricular nerve along the bony wall After sectioning the nerve, slight bleeding was usually noticed Seven subjects which belonged to this category were used for the subsequent statistical evaluation.

To approach the lateral ampullary nerve the horizontal portion of the facial nerve was exposed by opening the bony canal. When it was necessary the latero-posterior portion of the geniculate ganglion was removed Then, the superior posterior bony wall of the geniculate ganglion was gently drilled to expose the lateral ampullary nerve An extremely fine pick was used to cut the nerve. Seven monkeys with successful 75–100% nerve section were processed for statistical analysis.

Postoperative threshold measurement

The procedure of the postoperative rail threshold testing was identical to that of preoperation Animals were continuously tested until their rail thresholds reached the preoperative level for a minimum of three consecutive trial days.

Morphology

Upon the completion of acquisition of functional data, all animals were sacrificed by means of intravital cardiac perfusion. Temporal bones were removed and processed according to the standard preparation technique Serial horizontal sections were made at 20 micron thickness, one out ten sections were stained in hematoxylin-eosin, and examined by light microscopy

Statistics

For the statistical analysis, the following were used (1) the number of trial days of basic training, and threshold testing days to reach the operable criterion (three consecutive trial days with the rail threshold of 1 000 rpm or a given rpm more than 900 rpm plateau, with a minimal number of falls during one test sequence), and (2) the number of trial days and calendar days before the subject regained the preoperative rail threshold level for the first time postoperatively The purpose of statistical analysis is twofold, namely (1) to confirm that the randomly assigned subjects were evenly distributed among different experimental categories, and (2) to compare the effect of selective ablation among three experimental categories postoperatively

RESULTS

The mean number of trial days to reach the operative criterion was 14 6 for S 15 4 for U" and 15 7 for L An analysis of variance

Table I

"S	Trial days	Calendar days	U"	Trial days	Calendar days	L	Trial days	Calendar days
A	3	3	H	8	10	O	5	7
B	3	3	I	9	11	P	4	9
C		2	J	5	9	Q	6	8
D	4	4	K	6	11	R	6	8
E	4	4	L	1	14	S	11	17
F	3	3	M	18	21	T	5	9
G	3	3	N	11	13	U	12	16
x	3 14	3 14		9.86	12.71		7.00	10.57



on postoperative trial days. While the results of this test approached significance (F (2, 18) = 2.912, $p < 0.1$), the Duncan's test clarified the relationship between the treatments, and demonstrated significant differences between the treatment mean of "S" and "U" and "L" ($p < 0.05$). Also, no significant difference could be detected between "U" and "L" with regard to trial days.

Subsequent morphological investigation confirmed the destruction of the target end organs (Figs. 2, 3) and nerves (Fig. 4). Also other vestibular end organs in sound ears were not involved morphologically. The extent of the surgical lesions within each experimental group was found to be slightly variable among different subjects, but the difference was minimal. All inner ear end organ structures of the other ears



Fig 3 A and B Photomicrographs show the inferior portion of the macula utriculi (*U*) from the unoperated ear (*A*) and the utricular nerve sectioned ear (*B*) from the same subject. The neurons are degenerated, and many vacuole formations in the maculi utriculi can be seen 17 days postoperation. Horizontal section, H & E staining. (*A*) ×77 (*B*) ×84

subject required to regain the preoperative rail threshold level is given in Table I

An analysis of variance on postoperative calendar days yielded a significant $F(2, 18) = 15.72$, $p < 0.01$ Duncan's multiple range test showed that the number of calendar days to regain the level of preoperative criterion was significantly less for subjects in "S" than for subjects in either "U" or "L" ($p < 0.001$) No significant difference was found between "U" and "L"

Another analysis of variance was performed

degrees of postoperative labyrinthine reaction had to be expected. However as far as the body equilibrium compensation is concerned, the difference which was caused by surgical maneuver can be considered to be minimal as long as the present rail test, which measures the subject's maximum ability of locomotion performance, is being used for functional measurement. Such a difference may be manifested if a more sensitive measurement maneuver is used.

The contribution from the lateral crista ampullaris toward the maintenance of body equilibrium function was reconfirmed, by comparing the unilateral lateral ampullary nerve section and the unilateral utricular nerve section group. The difference between these two groups was not significant. However the trend demonstrated the longer compensation time after utricular nerve section, when compared to that after the lateral ampullary nerve section.

After unilateral utricular nerve section, the monkey has a systemic imbalance caused by the ablation of spontaneous discharge. In addition, the animal is deprived of unilateral utricular input (during his locomotive performance) which has a definite role in assisting the body equilibrium maintenance. Similar deprivation of the saccular input, if it is contributing toward the body equilibrium maintenance, should be considered. After unilateral lateral ampullary nerve section, in addition to the ablation-resulted systemic imbalance, the animal also suffers from the existence of horizontal beating postoperative nystagmus which biases his visual equilibrium cue, and also changes from time to time because of the oculomotor compensation along the time course. Also the inner ear was not opened by this operation procedure and therefore there should not be any direct labyrinthine reaction. Thus, in a strict analytical sense, the quantitative comparison of ablative effect of these two vestibular end organs by the present behavioral functional measurement has certain limitations due to the above described coexisting factors. However in a bionomical synthetical sense, these postoperative status represent the different postablative systemic dysequilibrium.

ZUSAMMENFASSUNG

Unter Anwendung des früher beschriebenen Schienenversuchs mit Totenkopfaffen wurde der Zustand nach der Operation von einseitiger sacculärer Macula Entfernung, einseitiger utrikulärer Nervensektion und einer lateralen Quersektion des ampullären Nerven [illegible] bemessen und statistisch verglichen.

Durch ein statistisches Verfahren wurde gleichfalls bestätigt, dass die freie Wahl von Subjekten gleichmässig verteilt war unter verschiedenen Versuchskategorien und daher war der [illegible] kategorisch-statistische Vergleich des Zustandes nach der Operation gültig.

Der minimale Beitrag der sacculären Macula zur Unterhaltung des körperlichen Gleichgewichtes wurde wieder bestätigt. In so weit wie das gegenwärtige Versuchsverfahren angewandt wird, wurde nur ein sehr geringer dominierender Beitrag der lateralen Crista ampullaris gefunden im Vergleich mit dem Beitrag der utrikularen Macula, begründet auf den unter sich kategorischen Vergleich, obwohl der Unterschied statistisch nicht bedeutend war. Die utrikulare Macula ist wahrscheinlich das wichtigste vestibulare Endorgan zur Erhaltung der körperlichen Gleichgewichtsfunktion.

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Versteegh, C. 1927. Ergebnisse partieller Labyrinthexstirpation bei Kaninchen. *Acta Otolaryngol* (Stock.) *11* 393.



Fig 4 This photomicrograph exhibits horizontal-sectional view of the macula utriculi (*U*) and lateral crista ampullaris (*L*) from a squirrel monkey whose lateral ampullary nerve was surgically sectioned. Macula utriculi and its nerve are morphologically intact. All neurons innervating lateral crista ampullaris are degenera Neuroepithelium of lateral crista ampullaris is flatte and some hair cells are lost. 1 days post operati H & E staining. 66.

in all experimental subjects were found to be morphologically intact

DISCUSSION

The results of postoperative intercategoric comparisons of "S" vs U and S" vs. L" indicate that the analysis of calendar day means demonstrates a clearer and statistically significant difference when compared against means of trial days The number of calendar days should be used for this sort of analysis (i e between experimental groups) insofar as the body equilibrium compensation requires a certain length of time inherent to the lesion probably regardless of the number of trials during that time period

Previously the minimal body dysequilibrium (locomotive) in squirrel monkeys was reported after unilateral saccular macula destruction when the body equilibrium function was measured the squirrel monkey rail test (Igarashi 197 Stepwise experimental controls, which includ routine stapedectomy and the saccular me brane rupture demonstrated minimal surgic involvement by these procedures A subseque report demonstrated severe locomotive dysequ librium after the unilateral utricular nerve sectio without exception (Igarashi et al 197?) B utilizing scattergraphs, the difference in bo equilibrium compensation after unilateral utri ular nerve section and unilateral saccul macula destruction was demonstrated In th present study by using a statistical procedure a significant difference between these two experi mental categories was well documented

The extent of surgical lesions was slightl varied among different subjects because of ana tomical and surgical variability Also different



Fig. 1. Sensory hairs are present i most hair cells of the ampulla.

formed to section the saccular nerve to complete the saccular nerve section, the route through the oval window was selected. Although total hearing loss resulted, his dizziness attacks disappeared.

MATERIALS AND METHODS

The approach to the inner ear was through the suprafacial root. The bony wall was thinned by the drill and opened by the chisel. The lateral and the anterior ampullae and the utricle were exposed. Those were removed by a cupforceps.

The tissue fragments obtained were immediately fixed in 6.25 glutaraldehyde solution with phosphate buffer (pH 7.4) at 4 C for 90 min. Then, the specimens were briefly rinsed with phosphate buffer (pH 7.4) at 4 C, and post-fixed in 1 osmic acid with phosphate buffer for 90 min. After dehydration with graded alcohol and acetone, the materials were embedded in Epon 812. The polymerized Epon blocks of the specimens were sectioned on a glass knife with a Porter Blum Ultramicrotome. The sections were stained with uranyl acetate and lead citrate and examined with a Hitachi HU-11E electron microscope with a magnification range of 1300 to 27 000.

RESULTS

The light microscopic examination revealed that the specimens removed during surgery were the utricle and ampullae. The ampullae were anterior and horizontal, but it was not determined which ampulla was horizontal. The utricle was confirmed by the presence of the otolithic membrane.

Under electron microscopic examination, type I type II hair cells and supporting cells were observed in the sensory epithelium. Most of the hair cells of the macula utriculi and crista ampullaris retained sensory hairs (Fig. 1), and a few hair cells were observed not to have sensory hairs. The remaining hairs were rising either straight or bent. Most hair cells showed normal subcellular structures (Figs. 2, 3*a* and 3*c*).

The mitochondria appeared healthy. There were some hair cells, however, with vacuoles in the cytoplasm (Figs. 2 and 3*b*). Fig. 2 illustrates a healthy type I hair cell showing a synaptic bar and a pathologic type I hair cell with vacuoles and dark inclusions. The dark inclusions were considered to be lipofuscin granules. Lipofuscin was found distributed in most hair cells, supporting cells, transitional cells and dark cells. Nerve endings and fibers did not contain lipofuscin. The lipofuscin was localized around the subsurface areas of the supporting cells and in the supranuclear portions of type I and type II hair cells.

The nerve chalices had a normal structure and the mitochondria were not pathological (Figs. 2 and 3). Besides the synaptic bodies, synaptic invaginations and thickening of the synaptic membranes were observed (Fig. 3*c*). The efferent nerve endings were seen to synapse with the nerve chalice (Fig. 3*d*). The nerve endings contained many healthy mitochondria.

The hair cells with pathologies like vacuoles or shrinkage of the cytoplasm were sparsely distributed throughout the sensory epithelia. The distribution of the pathological hair cells in the utricle was more general than in the ampullae. Cytoplasmic protrusion of the supporting cells was a common finding in both utricle and ampullae.

Acta Otolaryngol Suppl 330 100-106, 1975

ELECTRON MICROSCOPIC OBSERVATIONS OF THE UTRICLE AND AMPULLAE IN A CASE OF DIZZINESS OF SUSPECTED SACCULAR ORIGIN

Tetsuo Ishii and Jun-Ichi Suzuki

From the Department of Otolaryngology Teikyo University School of Medicine Tokyo, Japan

Abstract Electron microscopic observation was reported on the utricle and ampullae of a case, a 36-year-old male, with dizziness attack due to suspected saccular origin. After the removal of the utricle and ampullae, the dizziness recurred, and finally the saccular nerve section relieved the dizziness attack of this case. So the actual lesion was localized in the saccule and was not in the specimens obtained at the first surgery Though most of hair cells appeared normal, there were a few with many vacuoles or shrinkage of the cytoplasm distributing sparsely throughout the sensory epithelia. The distribution of the pathological hair cells in the utricle was more general than in the ampullae. The sensory hair cells without pathology and the presynaptic structures were similar to those found in the experimental animals. Nerve and nerve endings showed normal structures. The findings may be physiological at this age group or an extension of the pathology of the dizziness-causing lesion.

Electron microscopic studies of human vestibular labyrinth have been done on specimens obtained either from cadavers or from patients who had undergone surgery for Ménière's disease. In the previous paper (Suzuki et al 1974), a case of suspected sacculogenic dizziness was reported This patient a 36-year-old male, complained of repeated dizziness attacks with tinnitus. The patient underwent three times selective ablation of the labyrinthine endorgans. After saccular nerve section the dizziness terminated During the first operation the utricle and ampullae were removed and the specimens were extended to the electron microscopic evaluation The purpose of the present paper is to report the electron microscopic findings in the vestibular labyrinth of the case and to correlate the morphology to the clinical diagnosis. It should be noted that the specimens did not include the saccule which were believed to be the location of the lesion.

This work was partly supported by U.S.P.H.S. Research Grant No. NS 1041-

CASE REPORT

A 36-year-old male visited our clinic with a complaint of frequent attacks of dizziness and tinnitus in the right ear His dizziness was vibratory in the vertical direction and was always accompanied by tinnitus. These attacks began four years prior to his admission. A slight hearing loss on the right was found Calorization revealed a decreased response on that side. Although equilibrium disturbances were slight, there was some falling tendency to the right Under Frenzel glasses, a fine direction-fixed *positional and positioning nystagmus* was seen directed to the left On the basis of the neurological examinations, and also from the fact that Xylocaine application into the right tympanic cavity temporarily abolished the dizziness and tinnitus, an operation was performed on the right inner ear The utricle and two ampullae were removed via the supra-facial route and the specimens were examined with an electron microscope

The patient was relieved from the dizziness attacks and the hearing was restored The recurrence of the dizziness began gradually a month and a half after the first operation A second surgical procedure was the saccular nerve section through the supra-facial route which was not successful, the dizziness reappearing one week after surgery One month after the second operation, the third operation was per



Fig. 1. Sensory hairs are present in most hair cells of the ampulla.

formed to section the saccular nerve. .o complete the saccular nerve section, the route through the oval window was selected. Although total hearing loss resulted, his dizziness attacks disappeared.

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The mitochondria appeared healthy. There were some hair cells, however, with vacuoles in the cytoplasm (Figs. 2 and 3b). Fig. 2 illustrates a healthy type I hair cell showing a synaptic bar and a pathologic type I hair cell with vacuoles and dark inclusions. The dark inclusions were considered to be lipofuscin granules. Lipofuscin was found distributed in most hair cells, supporting cells, transitional cells and dark cells. Nerve endings and fibers did not contain lipofuscin. The lipofuscin was localized around the subsurface areas of the supporting cells and in the supranuclear portions of type I and type II hair cells.

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Fig 2 Type I hair cells of the ampulla. The hair cell on the left looks normal, while on the right vacuoles and dark inclusions (lipofuscin) are observed. *C* Chal *SB* synaptic bar

In Fig. 4 a type II hair cell is shown from the crista ampullaris. The cytoplasm of the hair cell contained a few vacuoles, and the thicken ing of the synaptic membranes was observed. Mitochondria of the nerve endings appeared normal. Some of these nerve endings showed healthy synaptic vesicles.

The nerve fibers consisted mostly of myelinated fibers and these showed normal structures (Fig. 5*a*). Some of the nerve fibers were found to show minor pathologies (Fig. 5*b*) These changes consisted of shrinkage of the axoplasm swollen mitochondria in the axon and disorganization of the myelin There was no abundant loss of fibers Degeneration of the axon was rarely found In places, some banded structures were present in the perineural tissues (*Fig. 5b*).

The dark cells showed marked cytoplasmic protrusions. Various kinds of vacuoles were seen in the subsurface areas. These dark cells also showed an electron-dense cytoplasm at the base they formed complicated cytop mic infoldings (Fig. 6) Huge lipofuscin gran were observed within the cells. Some of th were localized within large vacuoles (Fig. These lipofuscin granules consisted of 3 differ types, i.e. highly electron-dense small granu structure less electron-dense amorphous str tures and lipid like droplets (Fig 6) Th seemed to be no pattern in the distribution these granules within the cell

DISCUSSION

In this particular case extensive vacuolizati was not found which was usually observed the hair cells of Ménière s disease (Pietranto & Iurato 1960 Litton & Lawrence 1961 Ir land & Farkashidy 1963 Hilding & Hous



Fig. 3. Type I hair cells of ampulla. (*a*) A normal type I cell. There are no mitochondrial changes. (*b*) Hair cells with vacuolization distribute sparsely in the sensory epithelium. (*c*) Synaptic invaginations. (*d*) Two efferent nerve endings (*E*) attach to the chalice (*C*). *H*: Type I hair cell.

1964; Friedmann et al., 1963 and 1965). This case did, however, show a diffuse scattering of hair cells that had less extensive vacuolization within the cytoplasm. Considering that dizziness attacks disappeared after saccular nerve sectioning, the lesion was assumed to be in the saccule. The authors, therefore, did not expect causative lesion in the utricle and ampullae. These findings are interpreted in two ways. The morphological findings of the utricle and ampullae are explained to be within the normal physiological limits of this age group. Another interpretation is that these findings in the utricle and ampullae are an extension of the pathology of the dizziness-causing lesion in the saccule.

The utricular and ampullary nerves appeared normal and the nerve endings showed intact structures. Presynaptic structures in the human inner ear were exactly the same as reported in the experimental animals. There were synaptic invaginations, synaptic bodies and thickened synaptic membranes. Though some of fibers were seen to show a mild degenerating pattern, this may be due to physiological aging (Bergström, 1973).

The banded structures, found in the peri-



Fig. Type I hair cells of the ampulla. The hair cell on the left looks normal, while on the right vacuoles and dark inclusions (lipofuscin) are observed. *C*, Chalice. *SB*, synaptic bar.

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In this particular case extensive vacuolization was not found, which was usually observed in the hair cells of Ménière's disease (Pietrantoni & Iurato, 1960; Litton & Lawrence, 1961; Ir[e]land & Farkashidy, 1963; Hilding & House



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The banded structures, found in the peri-



Fig 4 Several nerve endings contact with the type II hair cell. Thickened areas of synapses are observed. The mitochondria and synaptic vesicles of the nerve endings are preserved well, while vacuoles are seen in the cytoplasm of the hair cell.

neural tissues, were already reported from inner ear specimens of Ménière s disease (Hilding & House, 1964 Friedmann et al 1963 and 1965 Kimura & Schuknecht 1970) These structures possibly were not related to the pathology of Ménière s disease

In the reports of Ménière s disease, the most common findings were loss of sensory hairs, extensive vacuolization of hair cells, the presence of dark inclusions and well-preserved nerve endings A hypothesis attempting to explain the mechanism of vertiginous attacks cited the presence of pathological hair cells in normal cyto-neural junctions (Pietrantoni & Iurato, 1960) Since the dark inclusions were known to exist in the membranous labyrinth of cadavers (Kimura et al 1964 Takahashi 1971), the inclusions were identified as lipofuscin, an age-dependent, "wear and tear" pigment (Ishii et al., 1967). This lipofuscin was not found in the inner ear of 2-day-old baby but it began to appear in 6-year-old child and was increasing in size and number according as ages (Ishii et al., 1967).

In the inner ear of the present case (36-year old) a considerable amount of lipofuscin was present The fact that this lipofuscin was found in the dark cells indicates that the dark cells perform an active secretory and/or absorptive function and are filled with vesicles and lysosomes. Lipofuscin is thought to be the final stage of a lysosome. The inner ear is presumed to provide an environment where the lipofuscin easily accumulates.



Fig. 5. Most nerve fibers show good myelinated fibers in the ampullary nerve (*a*), but shrinkage of axoplasm and mitochondrial swelling in the axon in some portion of the utricular nerve fibers (*b*). Banded structures are seen in the perineural tissues.

Fig. 6. The dark cells contain huge vacuoles in which varying form of dark inclusions are observed. All of these are considered to be lipofuscin. Cytoplasmic infoldings are seen (arrows).

ZUSAMMENFASSUNG

Die elektronenmikroskopische Beobachtung des Utriculus und der Ampullen eines 36-jährigen Mannes, der vom Schwindel belastet ist dessen Ursprung von einer saccularen Schädigung stammt, wurde vorgelegt.

Zwei Monate nach der Resektion des Utriculus und der Ampullen brach der Schwindelanfall wieder aus. Schliesslich trat eine Besserung durch die Resektion des Sacculus ein, auf die Klage des Patienten hin. Die aktuelle Läsion wurde dabei im Sacculus lokalisiert, sie war im Material bei erstem Eingriff nicht bemerkt worden.

Obwohl der grosste Teil der Haarzellen normal erschien, gab es eine Minderzahl von Haarzellen mit vielen Vakuolen oder zytoplasmatischer Einschränkung, die im sensorischen Epithel einzeln verstreut waren. Die Ausstreuung dieser pathologischen Haarzellen kamen im Utriculus häufiger vor als in den Ampullen. Die sensorischen Haarzellen ohne Pathologie und prasynaptische Struktur hatten Ähnlichkeit mit den Haarzellen, die bei Tieren experimentell gefunden wurden Die Nerven und Nervenendigungen zeigten normale Struktur Solche Befunde in dieser Altersgruppe könnten physiologischer oder als den Schwindel hervorrufenden Läsion von pathologischer Art sein.

ACKNOWLEDGEMENT

The authors wish to express their thanks to Mr D W Hughes for his advice on the English language.

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DIE LÄSION DES VERTIKALEN SYSTEMS UND DIE LÄSION DES HORIZONTALEN SYSTEMS IM OPTOKINETISCH VESTIBULÄREN SYSTEM

Eiji Sakata und Kunio Takahashi

Aus der Hals–Nasen–Ohrenklinik des Krankenhauses, Tokio-Rosai, Tokio, Japan

Abstrakt. Eine Betrachtung der Symptome von Schwindel und Gleichgewichtsstörung, wie sie bei einer Läsion des optokinetisch-vestibulären Systems auftreten, ließ bei getrennter Betrachtung der Läsion des vertikalen Systems und der des horizontalen Systems erkennen, daß die zu beobachtenden Symptome sich ziemlich *einheitlich ordnen* lassen. Im ersteren Fall liegt nämlich die Läsion im Zentrum des Hirnstammes bzw. des Kleinhirns oder symmetrisch bzw. beidseitig des peripher-vestibulären Systems, oder aber sie tritt diffus auf. Im Gegensatz *dazu tritt sie im letzteren Fall* bei den obigen Stellen einseitig rechts oder einseitig links auf. Die Läsion des vertikalen *Systems* ergibt sich, daß das optokinetisch-vestibuläre System direkt oder indirekt beidseitig lädiert ist, und angefangen von Schwindel und *Gleichgewichtsstörungen*, die verspürt werden, sind die in Augen sowie *Extremitäten* und *Rumpf auftretenden Symptome* symmetrisch und äußern sich hauptsächlich auf der Ebene des Systems des vertikalen semicirculären Kanals (der sagittalen Ebene). Im Gegensatz dazu ist es bei Läsionen des horizontalen Systems die Regel, daß sich die Symptome auf der Ebene des horizontalen semicirculären Kanals äußern.

Bei der Diagnose von Patienten, die sich über Schwindel oder Gleichgewichtsstörungen beklagen, wurde bis jetzt das Hauptaugenmerk darauf gerichtet, in welchem Organ das Übel positioniert ist, wie z. B. Hirnstamm oder Kleinhirn, VIII. Nerv oder aber Endorgan des Innenohres. Vom Standpunkt der klinischen Diagnostik her gesehen ist dies eine äußerst bedeutsame Tatsache.

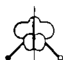
Auf der anderen Seite bestand allerdings bisher die Tendenz, daß bei Untersuchung und Befund *nicht nur bei den subjektiven Symptomen*, sondern auch bei den Symptomen, die in den Augen oder in den Extremitäten auftreten, je nach Fall separat und voneinander unabhängig Beobachtungen gemacht wurden, und *daher nicht unbedingt genügende* Beachtung einer Reihe von Wechselbeziehungen geschenkt wurde, die im Verborgenen zwischen den einzelnen Untersuchungen bestehen. *So wurde oft*, auch nach gefällter Diagnose, keine systematische Analyse der Gesamtheit der aufgetretenen Symptome vorgenommen, und auch der Weiterentwicklung der Diagnostik ein ungewolltes Hindernis in den Weg gestellt.

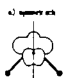
Wenn wir nun die Sache einmal von einem *etwas anderen Standpunkt aus betrachten, d. h.* von den verschiedenen Symptomen aus, die bei den Fällen von Schwindel oder Gleichgewichtsstörungen beobachtet werden, können in Verbindung mit dem Problem, ob die Läsion des optokinetisch-vestibulären Systems zentral ist oder aber peripher gestört ist, je nachdem ob die Läsion *einseitig oder beidseitig ist, bei dem* entsprechenden Befund der Untersuchung eine Reihe von Besonderheiten beobachtet werden, die sich *ziemlich einheitlich klassifizieren lassen*. Mit anderen Worten, ganz gleich, ob das Übel zentral oder peripher gelagert ist — im Fall einer beidseitigen *Läsion* z. B. sind die Symptome einander sehr ähnlich.

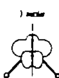
DIE LÄSION DES VERTIKALEN SYSTEMS UND DIE LÄSION DES HORIZONTALEN SYSTEMS

Als Läsion des horizontalen Systems haben wir solche Fälle angenommen, wo bei einer Läsion des optokinetisch-vestibulären Systems das Übel

Diese Abhandlung soll dem sehr verehrten Professor Dr. Dr. h.c. Tadashi Fukuda anläßlich seines Abschieds von seinem Amte herzlich gewidmet sein.







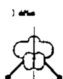


Abb 1 Die Klassifikation der Läsionen.

einseitig auf einer von beiden Seiten positioniert ist.

Die Läsion des vertikalen Systems ist dagegen gegeben, wenn eine Mehrzahl von Läsionen rechts-links-symmetrisch zur gleichen Zeit oder rechts und links diffus oder buchstäblich im mittleren Teil existiert wo das optokinetisch-vestibuläre System ob nun direkt oder indirekt, beidseitig beeinflußt wird (Abb 1)

RESULTATE UND ÜBERLEGUNGEN

Wenn wir zunächst einmal die subjektiven Symptome bei der horizontalen Läsion unter suchen d. h bei einseitigem Befallensein des Innenohrs (z. B Morbus Ménière oder Labyrint hentzündung) oder Akustikustumor im Früh stadium weiterhin bei Arten von Krankheiten des Kleinhirns oder Hirnstammes (wie z. B Blutung der Kleinhirnhemisphäre oder Wallen bergsches Syndrom) erscheint der Schwindel auf der frontalen Ebene oder der horizontalen Ebene der Schwindel dreht sich im Uhrzeiger sinn oder im Gegenuhrzeigersinn man selbst oder die Umgebung fließt nach links oder rechts. Dagegen ist es bei Läsion des vertikalen Systems (z. B plötzlicher Durchblutungsläsion der Arteria basilaris oder vaskuläre Läsion des Kleinhirnwurms) nicht selten daß der Schwindel sich um die sagittale Ebene, d h vor oder zurück, dreht oder Schwankungen nach oben oder unten gefühlt werden. Nervensymptome, wie Kopfschmerz u a., sind bei der Läsion des vertikalen Systems symmetrisch während sie bei der des horizontalen Systems einseitig verlaufen (Tabelle I)

Nun möchten wir unsere Überlegungen auf die objektiven Symptome die in den Extremitäten und im Rumpf auftreten, ausdehnen

Bei der Läsion der vertikalen Systems ist allgemein eine Gleichgewichtsstörung zu beobachten die sich hauptsächlich nach vorwärts- oder in rückwärtiger Richtung auswirkt, wie ich falle nach vorne oder ich falle rück wärts" Mit anderen Worten ist dies eine Gleichgewichtsstörung hauptsächlich der sagittalen Ebene die eine enge Beziehung zur Ebene des vertikalen semicircularen Kanals aufweist. Auch die Ataxie tritt beidseitig auf und in der Regel sind die Läsion von Reflex und Sensibilität ferner auch das Nachlassen der Muskelkraft, beidseitig. Verglichen dazu äußert sich bei der Läsion des horizontalen Systems die Gleichgewichtsstörung im wesentlichen seitwärts, und Ataxie wie auch die Läsion von Reflex und Sensibilität und muskuläre Hypotonie treten einseitig auf (Tabelle II)

Als nächstes möchten wir eine Untersuchung der Symptome die im optokinetisch-vestibulären System zu beobachten sind vornehmen

Bei der Läsion des vertikalen Systems tritt

Tabelle I *Die subjektiven Symptome*

	Läsion	
Symptom	Vertikales System	Horizontales System
Schwindel	Hauptsächlich in der sagittalen Ebene drehen	Hauptsächlich in der frontalen Ebene drehen
Gleichgewichtsstörung	Hauptsächlich in der sagittalen Ebene	Hauptsächlich in der frontalen Ebene
Andere Nervensymptome	Mehr symmetrisch mittler	Mehr einseitig

nicht selten ein vertikaler Spontannystagmus nach dem oberen Augenlid bzw. nach dem unteren Augenlid auf, verglichen dazu ist es bei der Läsion des horizontalen Systems die Regel, daß ein horizontaler Spontannystagmus, bzw. ein horizontalrotierender gemischter Spontannystagmus beobachtet wird (Frenzel, 1955, Kornhuber, 1966, Sakata, 1966). Auch bei Betrachtung des Lagenystagmus und Lagerungsnystagmus zeigt sich, daß bei der Läsion des vertikalen Systems häufig ein vertikaler Lagenystagmus oder Lagerungsnystagmus zu beobachten sind, und ferner ein richtungswechselnder aufwärtsschlägiger Lagenystagmus (bei Bewegung des Kopfes des Patienten nach rechts unten wird es ein Nystagmus nach links, bei Bewegung nach links unten wird es ein Nystagmus nach rechts) festzustellen ist, dagegen ist bei Läsion des horizontalen Systems ein richtungsbestimmter Lagenystagmus zu beobachten (Sakata, 1966, 1971). Auch ist, besonders bei einseitigen Innenohren-Fällen, nicht selten ein den Schwindel begleitender rein rotierender Lagenystagmus und ferner ein rein rotierender gegenläufiger Lagerungsnystagmus zu beobachten (Stenger, 1955, Sakata u. a., 1966). Der blickabhängige Nystagmus ist bei der Läsion des vertikalen Systems, sei es nun ein paretischer Nystagmus, der von einer Läsion des Hirnstammes herrührt, oder ein dysmetrischer Nystagmus, der auf Grund einer Läsion des Kleinhirnes auftritt, oder aber eine Läsion, die auf einer Fixationsstörung wie idiopathischem kongenitalem Nystagmus beruht, mehr oder weniger rechts-links-symmetrisch. Im Vergleich dazu ist er bei einer Läsion des horizontalen Systems immer einseitig und unsymmetrisch (Tabelle III).

Tabelle II. *Die Symptome an dem Rumpf und den Extremitäten*

Symptom	Läsion	
	Vertikales System	Horizontales System
Gleichgewichtsstörung	Hauptsächlich in der sagittalen Ebene (nach vorne bzw. hinten)	Hauptsächlich in der frontalen Ebene (nach seitlich fallen bzw. deviieren)
Ataxie	Hauptsächlich beiderseitig	Hauptsächlich einseitig
Reflex, Sensibilität, Muskelkraft usw.	Hauptsächlich beiderseitig	Hauptsächlich einseitig

Tabelle III. *Der Nystagmus*

Nystagmus	Läsion	
	Vertikales System	Horizontales System
Spontannystagmus	Vertikal od. schräg	Horizontal od. horizontal-rotierend
Lagenystagmus	Vertikal, schräg, oder richtungswechselnd aufwärts-schlägig	Richtungsbestimmt
Lagerungsnystagmus	Vertikal	Horizontal, horizontal-rotierend od. rein-rotierend u. gegenläufig
Blicknystagmus	Symmetrisch blickparetisch blickdysmetrisch	Asymmetrisch od. manchmal einseitig

Ferner möchten wir die motorische Störung betrachten, die bei den Augen hervorgerufen wird.

Was die konjugierte Blickbewegung angeht, so wird durch Läsion des Hirnstammes, besonders der des Pons, die horizontale Blickbewegung gestört, während bei Läsion des Mittelhirns hauptsächlich die vertikale Blickbewegung gestört wird. Es ist gezeigt worden (Bender et al., 1964, Sakata et al., 1971), daß im ersteren Fall die Läsion der paramedianen Brückenhaube (paramedian pontine tegmentum), im letzteren eher die Läsion von Hinterkommissur und Pretectum als die des Colliculus superior einen großen Einfluß haben. In solchen Fällen ist im ersteren wie im letzteren Fall die sog. „schnelle Augenbewegung" wie die schnelle Phase des Nystagmus oder die sakkadierende Augenbewegung etc., empfindlicher gegen diese Läsionen, kann in einem früheren Stadium Störungen empfangen als die „langsame Augenbewegung" wie die Blickfolgebewegung oder

Tabelle IV *Die andere Bewegungsstörung an den Augen*

Befund	Läsion	
	Vertikales System	Horizontales System
Blick	Vertikal	Horizontal
Optokinetischer Nystagmus	Beiderseitig symmetrisch	Einseitig asymmetrisch
Optokinetischer Nachnystagmus	Bei Kleinhirn verlängert. Bei Hirnstamm od. periph. vest. gehemmt	Seitendifferenz
Blickfolge	Symmetrisch	Asymmetrisch. Bei periph. vest. normal

die tonische Abweichung, und erholt sich sich auch langsamer als diese

Daher ist es auch bei Prüfung des optokinetischen Nystagmus so daß bei Läsion des vertikalen Systems die Störung beidseitig und symmetrisch erfolgt, während sie bei Läsion des horizontalen Systems (bei Läsion von Innenohr oder Kleinhirn selbst tritt so leicht keine starke Störung auf bei Läsion des Hirnstammes dagegen treten sehr deutliche Störungen auf) einseitig und unsymmetrisch erfolgt Bei Läsion *des vertikalen Systems besonders bei Läsion* des oberen Hirnstammes (Mittelhirn) wird der optokinetische Nystagmus nach dem oberen Augenlid, bei Läsion des mittleren Hirnstammes (Pons) oder des unteren Hirnstammes (Medulla) wird der optokinetische Nystagmus nach dem unteren Augenlid gestört.

Auch beim optokinetischen Nachnystagmus haben wir fast die gleiche Situation bei Läsion des vertikalen Systems fällt eine deutliche beidseitige Hemmung auf bei Läsion des horizontalen Systems fällt eine links-rechts-Differenz auf während bei Läsion des Kleinhirns zeigt sie eine Überreaktion wegen Ausfalls der Hemmung auf das optokinetisch-vestibuläre System

Auch bei der Blickverfolgungsprüfung ist sie bei Läsion des vertikalen Systems symmetrisch, bei Läsion des horizontalen Systems fällt sie unsymmetrisch aus (bei peripher vestibulärer Störung tritt keine Läsion auf). Darüber hinaus, bei Läsion des Hirnstammes ist sie sakkadierend, bei Läsion des Kleinhirnes treten infolge von Hypermetrie und Hypometrie große Wellen auf (Sakata, 1973) (Tabelle IV)

MUSTERFÄLLE

A Beispiele für Läsion des vertikalen Systemes

Fall 1 K.J 61 Jahre männl Arzt dextromanuell

Hauptsymptome Kopfschmerzen, Schwindel, *Schwächegefühl an Gliedern Gleichgewichtsstörung.*

Familiengeschichte Von Hypertonie und Apoplexie belastet.

Anamnese Vor 25 Jahren Pneumonie seit 20 Jahren leidet er unter Hypertonie.

Status praesens Seit ungefähr 10 Jahren leidet er manchmal, hauptsächlich am frühen Morgen unter plötzlichen heftigen Hinterkopfschmerzen *Drehschwindel in der sagittalen* Ebene Brechreiz, Erbrechen, Lähmungsgefühl und Schmerz an beiden Armen. Die Häufigkeit dieses Anfalls 4–5 mal jährlich. Besonders bei einem *Anfall vor 6 Jahren wurde der allgemeine* Krampf mit obengenannten Anfällen begleitet, und der Tremor an den beiden Armen dauerte etwa eine Woche lang.

Vom 4 oder 5 Monat an nach diesem Anfall vor 6 Jahren, wankte er oft *vorwärts oder rückwärts* und allmählich wurde sein Gang gestört Eine Zeitlang danach bekam er Anfälle jedoch nicht so oft aber seit etwa zwei Jahren tritt der Anfall wider auf Ein blutdrucksenkendes Mittel und Krampf*mittel wurden eingenommen doch* wurde die Krankheit nicht besser Vor drei Monaten bekam er einen ziemlich heftigen Anfall und dabei entdeckte sein Freund ein Arzt, den Nystagmus.

Prüfungsresultate Blutdruck 165–112. Augenhintergrund, K–W II Grad. Die beiderseitigen leichten Stauungspapillen sind erkennbar In aufgerichteter Haltung fällt der Patient beim

Augenschließen leicht nach hinten. Beim Tretversuch hat er eine Falltendenz vor- und rückwärts. Kein Kleinhirnsymptom. Auch kein Hirnnervensymptom. Der Sehnenreflex steigert sich beiderseitig ein bißchen. Kein pathologischer Reflex ist sichtbar. Der zerebrospinale Druck und dessen Eigenschaft sind normal.

Wenn der Patient ohne Brille nach vorne sieht, ist der kurzperiodisch, unregelmäßig *richtungsalternierende horizontale* Nystagmus erkennbar. Beim Auf- und Niederblick wird dieser Nystagmus ein *vertikaler* Nystagmus in Unteraugenlidrichtung, beim Blick nach rechts und links wird er ein Nystagmus in der *rechten* und *linken* Blickrichtung, und in beiden Fällen ist keine Veränderung der Richtung zu erkennen. Bei Benutzung der Leuchtbrille ist kein Nystagmus erkennbar. Bei der Lageprüfung ist der richtungsalternierende aufwärtsschlägige Nystagmus festzustellen, und auch bei der Kopfhängelage wird ein *vertikaler* Nystagmus ausgelöst. Bei der Lagerungsprüfung ist ein feinschlägiger *vertikaler Nystagmus sichtbar*. Aber dabei *klagte* der Patient gleichzeitig über *ein* starkes Schwindelgefühl. Die beiderseitige Enthemmungshemmung des optokinetischen Nystagmus. Die Motorik der Blickzielverfolgung ist *symmetrisch* ziemlich gestört.

In CAG und VAG ist keine bemerkenswerte Veränderung sichtbar, aber bei PEG befindet sich ein symmetrisches Vergrößerungsbild der beiderseitigen Gehirnkammer und des Ventriculus tertius. Durch die Myodil-Ventrikulographie ist ein Befund, der vielleicht als leichter Schattendefekt im *hinteren Bereich* des *Ventriculus* quartus zu betrachten ist, erhältlich.

Operationsbefunde: Da auch der Patient es wünschte, wurde die Kraniotomie durchgeführt. In der Kleinhirnhemisphäre wurde keine außergewöhnliche Veränderung festgestellt, aber *im Wurm* wurde die Atrophie betrachtet und besonders im Unterwurm war schon deren Spur vorhanden. Jedoch im Bereich des Oberwurms über Mittelwurm war ein außergewöhnlicher Vorwölbungsteil sichtbar. Durch die *Punktion* wurde ca. 1,5 cc gelbe Flüssigkeit aspiriert. Beim ... war ein kleines Blutgerinnsel *er*kennbar. Die Cystis wurde *mit physiologischer* Kochsalzlösung *genug gespült und ein* Teil der inneren Wand *experimentell* exzidiert. Pathohistologisch war *kein Befund* des Haemoangioms feststellbar.

Betrachtung: Bei diesem Fall wurde der Anfall langperiodisch wiederholt. Es ist offensichtlich, daß zwischen diesen Anfällen und den pathologischen Veränderungen am Wurm irgendeine Beziehung besteht. Es scheint mir, daß es eine enge Kausalität mindestens zwischen dem Anfall vor drei Monaten und dieser krankhaften Veränderung des Wurms, ferner dem eigenartigen Nystagmus, gibt. Aber ich kann leider nicht zu einer Folgerung gelangen, ob das Atrophiebild, das im ganzen Wurm betrachtet wurde, mit den lange wiederholten Anfällen zusammenhängt, oder ob diese Atrophie ein sogenanntes „Degenerationszeichen" ist und die Ursache dualistisch erklärt werden soll.

Fall 2: I.I., 54 Jahre, weiblich, Hausfrau, dextromanuell

Hauptsymptome: Schwankschwindel, Ataxie nach vor- *und rückwärts*, Gangstörung, Ohrensausen re. < li. und Schwerhörigkeit bds.

Familiengeschichte: Nichts Besonderes.

Anamnese: Geburt 5mal, Abortus 2mal, vor 35 Jahren Keratoparenchymatose.

Status praesens: Seit etwa 2 Jahren ist Ataxie vorhanden. Ihr Gang wird allmählich gestört, und sie wankt leicht *vorwärts oder rückwärts*. Vor 4 Monaten hatte sie plötzlich einen Schwindelanfall, der etwa 3 Stunden anhielt und von Übelkeit und Erbrechen begleitet wurde. Danach wurden die Gangstörungen deutlicher und *beidseitiges Ohrensausen und Schwerhörigkeit* traten auf. Von einem *Internisten wurde ihr gesagt*, daß Verdacht auf einen *Kleinhirntumor* bestehe.

Hauptresultate der Prüfungen: Blutdruck 154–94, K-W I-Grad, Rombergsches Symptom (+ +), *fällt vor- oder rückwärts*. Bei der Mannschen Prüfung zeigt sie starke Schwankungen, mit *unbestimmter* Fallrichtung. Kann nicht auf Zehenspitzen oder Fersen laufen. Beim Tretversuch *hat sie rückwärtige* Falltendenz. Wasser

Tabelle IV *Die andere Bewegungsstörung an den Augen*

Befund	Läsion	
	Vertikales System	Horizontales System
Blick	Vertikal	Horizontal
Optokinetischer Nystagmus	Beiderseitig symmetrisch	Einseitig asymmetrisch
Optokinetischer Nachnystagmus	Bei Kleinhirn verlängert. Bei Hirnstamm od. periph. vest. gehemmt	Seitendifferenz
Blickfolge	Symmetrisch	Asymmetrisch. Bei periph. vest. normal

die tonische Abweichung, und erholt sich sich auch langsamer als diese

Daher ist es auch bei Prüfung des optokinetischen Nystagmus so daß bei Läsion des vertikalen Systems die Störung beidseitig und symmetrisch erfolgt während sie bei Läsion des horizontalen Systems (bei Läsion von Innenohr oder Kleinhirn selbst tritt so leicht keine starke Störung auf bei Läsion des Hirnstammes dagegen treten sehr deutliche Störungen auf) einseitig und unsymmetrisch erfolgt Bei Läsion des vertikalen Systems, besonders bei Läsion des oberen Hirnstammes (Mittelhirn), wird der optokinetische Nystagmus nach dem oberen Augenlid bei Läsion des mittleren Hirnstammes (Pons) oder des unteren Hirnstammes (Medulla) wird der optokinetische Nystagmus nach dem unteren Augenlid gestört

Auch beim optokinetischen Nachnystagmus haben wir fast die gleiche Situation bei Läsion des vertikalen Systems fällt eine deutliche beidseitige Hemmung auf bei Läsion des horizontalen Systems fällt eine links-rechts-Differenz auf während bei Läsion des Kleinhirns zeigt sie eine *Überreaktion* wegen Ausfalls der Hemmung auf das optokinetisch vestibuläre System

Auch bei der Blickverfolgungsprüfung ist sie bei Läsion des vertikalen Systems *symmetrisch* bei Läsion des horizontalen Systems fällt sie unsymmetrisch aus (bei peripher vestibulärer Störung tritt keine Läsion auf) Darüber hinaus, bei Läsion des Hirnstammes ist sie sakkadierend, bei Läsion des Kleinhirnes treten infolge von Hypermetrie und Hypometrie große Wellen auf (Sakata, 1973) (Tabelle IV)

MUSTERFÄLLE

A Beispiele für Läsion des vertikalen Systemes

Fall I K I 61 Jahre männl Arzt dextromanuell

Hauptsymptome Kopfschmerzen Schwindel Schwächegefühl an Gliedern, Gleichgewichtsstörung.

Familiengeschichte Von Hypertonie und Apoplexie belastet

Anamnese Vor 25 Jahren Pneumonie seit 10 Jahren leidet er unter Hypertonie

Status praesens Seit ungefähr 10 Jahren leidet er manchmal, hauptsächlich am frühen Morgen, unter plötzlichen heftigen Hinterkopfschmerzen, Drehschwindel in der sagittalen Ebene Brechreiz, Erbrechen, Lähmungsgefühl und Schmerz an beiden Armen Die Häufigkeit dieses Anfalls 4–5 mal jährlich Besonders bei einem Anfall vor 6 Jahren wurde der allgemeine Krampf mit obengenannten Anfällen begleitet, und der Tremor an den beiden Armen dauerte etwa eine Woche lang.

Vom 4 oder 5 Monat an nach diesem Anfall vor 6 Jahren wankte er oft *vorwärts oder rückwärts* und allmählich wurde sein Gang gestört Eine Zeitlang danach bekam er Anfälle, jedoch nicht so oft aber seit etwa zwei Jahren tritt der Anfall wider auf Ein blutdrucksenkendes Mittel und Krampfmittel wurden eingenommen, doch wurde die Krankheit nicht besser Vor drei Monaten bekam er einen ziemlich heftigen Anfall, und dabei entdeckte sein Freund ein Arzt, den Nystagmus.

Prüfungsresultate Blutdruck 165–112 Augenhintergrund, K–W II Grad Die beiderseitigen leichten Stauungspapillen sind erkennbar In aufgerichteter Haltung fällt der Patient beim

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mann-Bluttest positiv Im linken Ohr besteht Verdacht auf das Hennebertsche Zeichen *Bei* der Calorischen Prüfung fällt *die Reaktion rechts wie links* deutlich ab Auch die kompensatorische Gegenrollung der Augen läßt auf *beiden* Seiten ziemlich nach *Was die Hör*schärfe angeht so zeigt sie auf *beiden Seiten* mittelgradige perzeptive Schwerhörigkeit. Mittels der Lagerungsprüfung wurde ein *mehr als* 10maliger *Vertikalnystagmus* nachgewiesen

Betrachtung Dies ist ein Fall bei *dem am* meisten Verdacht auf peripher vestibuläre Läsion auf *beiden* Seiten besteht, im besonderen auf beidseitige Innenohr Läsion alle Symptome zeigen die Eigenschaften der Läsion des vertikalen Systems.

B *Beispiel für Läsion des horizontalen Systems*

Fall 3 K S 23 Jahre männlich Kaufmann dextromanuell

Hauptsymptome Gangstörung, Ohrensausen re Sprachstörung und Handtremor re

Familiengeschichte und Anamnese Nichts Besonderes.

Status praesens Eine Nacht vor 5 Monaten hatte er einen Krampf am ganzen Körper mit 38 5 C Fieber Einige Tage danach verspürte er bei Körperbewegungen vom *rechten* Occipital zum Parietal hin einen pulsierenden Schmerz. Seit 3 Monaten hat er Ohrensausen auf der *rechten* Seite Seit mehreren Wochen fallen Gangstörungen auf und es besteht eine Fall*tendenz nach rechts* Sein *rechter* Hausschuh fällt vom Fuß oder beim Hinuntersteigen der Treppe strauchelt er auf dem *rechten* Fuß. Es kommt auch vor daß er seine Eßstäbchen, die er in der *rechten* Hand hält fallen läßt.

Hauptresultate der Prüfungen Beim Aufstehen besteht Fallneigung nach *rechts* Kein Einbeinstehen möglich Beim Tretversuch wankt er nach *rechts* Fast keine Stauungspapille vorhanden Sowohl bei Seitenblick links als auch bei Seitenblick rechts ist ein dysmetrischer *horizontaler* Nystagmus zu beobachten Bei der Lageprüfung wird sowohl bei Kopfposition des Patienten nach rechts unten wie auch bei Po*sition nach links* unten ein horizontaler Nystagmus hervorgerufen Bei der Lagerungsprüfung ist *ein nach links schräg* unten gerichteter Nystagmus zu beobachten Der optokinetische *Nystagmus* hat eine Seitendifferenz, er wird *lebhaft nach links* hervorgerufen aber es scheint, *in sowohl rechter als linker* Richtung, zumindest keine deutliche Läsion des okulomotori*schen Systems* zu bestehen Bei der Blickver*folgungsprüfung* kann eine dysmetrische Struk*tur beobachtet* werden. Weder Pyramiden-Symptom, Sensibilitätsstörung noch pathologi*scher Reflex sind* vorhanden, der Liquordruck ist im Anfangsdruck 130 H_2O nach Entnahme von 5cc ist der Enddruck 120 H_2O Pandy positiv

Betrachtung Unter Verdacht auf einen Tumor der *rechten* Kleinhirnhemisphäre führten wir VAG und PEG durch Durch Ausführung der Kraniotomie stellten wir ein in der rechten Kleinhirnsphäre einseitig existierendes Astrozytom fest und exzidierten es.

Dies ist ein Beispiel für Läsion des horizontalen Systems.

SUMMARY

Symptoms of vestibulo-ocular disturbances may be classified into two major groups *i.e., vertical plane and* horizontal plane disturbances

Vertical plane symptoms arise from midline lesions of the cerebellum or the brainstem and also from d ffuse or symmetrical lesions to either

Vertical plane symptoms also arise from lesions which simultaneously effect both peripheral vestibular systems.

Horizontal plane symptoms originate from a unilateral disturbance in the vestibular system

Thus, vertical plane symptoms indicate bilateral *disturbances and the* symptoms appear symmetrically in the eyes, trunk or extremities Vertical plane symptoms appear in the sagittal plane, or the plane of the vertical semicircular canals *On the other hand,* horizontal plane symptoms appear in the horizontal plane, *or the plane* of the horizontal semicircular canals.

DANKWORT

Zum Schluss möchten wir hier Herrn Prof Dr Dr h c *Shunshiro Kondo unsere herzliche* Dankbarkeit dafür bezeugen, daß er uns freundlich beraten und diese Abhandlung durchsehen hat.

rapidly over a one to two day period regardless of the presence or absence of dizziness.

The positional and positioning tests with ENG recording were performed as follows (Uemura, 1969). After examination of spontaneous nystagmus in the supine position, a patient was asked to roll his entire body over slowly first to the right side and then back to the supine position. The lateral position was maintained for one minute. Next he turned to the left lateral position in the same manner and then back to the supine position. Observation of nystagmus was made under Frenzel glasses and ENG recording was simultaneously conducted. The test was repeated with the eyes open in the dark and with the eyes closed. The positioning test was performed by seating the patient, having him lie down rapidly with his head hanging backward for 30 seconds, and then return to the sitting position. The test was observed under Frenzel glasses and was repeated with the eyes open in the dark.

Patients were retested as often as possible until disappearance of nystagmus. The average time of testing was 4.8 with the average interval of 7.2 days.

Positional nystagmus (PN) and positioning nystagmus (PGN) were differentiated from spontaneous nystagmus (SPN), which continued to be present with an almost similar intensity in the positional and positioning tests, and were further divided into the following subgroups.

1. *Direction-fixed PN*

A nystagmus first occurs or increases in intensity with a change in position. It persists for over 30 seconds as long as the new position is maintained. When the supine position is resumed, nystagmus disappears or decreases to its original intensity.

2. *Direction-changing PN*

When assuming the left or right lateral position a nystagmus, whose direction is opposite to that present in the supine or the other lateral position, persistently occurs. This PN is further subdivided into geotropic (divergent) or apogeotropic (convergent) type, depending on whether the quick phases are to the ground or away from the ground.

3. *Horizontal PGN*

A transitory nystagmus which is mainly horizontal may occur when the position is changed from the supine to the right or left lateral position, or when changed from the sitting to the head-hanging position. It usually reaches a peak in several seconds and gradually recedes or disappears.

4. *Vertical PGN*

A transitory vertical nystagmus may be induced by the positioning test. Its character is similar to those described above or it has peak strength immediately after the head-hanging position is assumed.

RESULTS

1. *Findings in the initial tests*

The interval between the date of the onset of vertiginous attack and the time of initial testing ranged from 1 to 25 days, the average being 6.1 days. All of the 31 cases had nystagmus at the initial testing.

Table I shows the incidence of various types of SPN and PN (or PGN). The direction of a nystagmus present in the supine position was toward the involved ear in 17 cases and toward the opposite ear in 10 cases. In the remaining 4 cases no nystagmus was present in the supine

Table I. Nystagmus findings at the initial testing PGN is shown in parentheses

	Nystagmus present in the supine position		Nystagmus absent in the supine position
	Toward the involved ear	Toward the opposite ear	
Spontaneous nystagmus	9	4	0
Direction-fixed PN	3	1	1 (1)
Direction-changing PN	5	5 (1)	3 (1)
Total	17	0	4

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TRANSITION OF NYSTAGMUS TYPES IN UNILATERAL LABYRINTHINE DISEASES

Takuya Uemura, Naohiro Yamaguchi and Emiko Iwashima

From the Department of Otolaryngology Tokyo Women's Medical College Tokyo Japan

Abstract In order to clarify changes in spontaneous and positional nystagmus which occurred during the course of peripheral labyrinthine diseases, 31 patients with Ménière's disease (17 cases), aural vertigo of unknown etiology (9 cases), and sudden deafness (5 cases) were tested repeatedly using ENG The testing of each case was made 4 8 times on the average with an average interval of 7.2 days. Twenty-four cases (77 4 %) showed more than two of the following four types which are listed in serial order of occurrence spontaneous (or direction-fixed positional) nystagmus toward the involved ear geotropic direction-changing positional nystagmus, spontaneous (or direction-fixed positional) nystagmus toward the opposite ear and apogeotropic direction-changing positional nystagmus. Thus, the above-mentioned order may be regarded as the uniform pattern in the nystagmus transition caused by acute unilateral labyrinthine diseases.

Positional and positioning tests have been recognized as essential for the diagnosis of vertigo and dizziness and are widely used as part of the routine examination of equilibrium function However diagnostic determination of the location of lesions on the basis of positional and positioning nystagmus has not yet been established despite the existence of extensive literature on animal experiments and clinical observations. One of the reasons for this obscurity seems to be that changes in the features of positional nystagmus during the course of a disease have been disregarded

The purpose of the present report is to describe the transition in the types of nystagmus following acute unilateral labyrinthine diseases and to disclose the regularity of these patterns.

MATERIALS AND METHODS

The positional and positioning tests using electronystagmographic (ENG) recording were performed on 189 patients twice or more during the course of disease for the seven year period from May 1963 to April, 1970 at the Department of Otolaryngology Tokyo Women's Medical College There were 45 patients who demonstrated the transition of nystagmus direction, after those with suspect of central vestibular lesions were excluded For the purpose of this study 31 cases were selected on the basis of the following criteria they had a clear time interval between the data of the onset of vertiginous attack and the time of examination and the involved ear was determinable by means of the caloric or audiometric tests.

The 31 cases consisted of 15 males and 16 females, ranging in age from 19 to 60 with an average of 36. They included 17 cases of Ménière's disease, 9 cases of aural vertigo of unknown etiology and five cases of sudden deafness. Ménière's disease was defined as a disorder with repeated vertiginous attacks accompanied by auditory symptoms. Absence of otitis media, head trauma or arteriosclerosis and of any cranial nerve sign other than that of the eighth cranial nerve was a prerequisite for the diagnosis of Ménière's disease A patient was diagnosed as aural vertigo of unknown etiology when he complained of clear vertigo and the presence of peripheral labyrinthine lesion was demonstrated by a significant reduction of caloric response or by audiometric findings but no evidence of neighboring brainstem involvement was concluded on the basis of neurological examination. A patient was diagnosed as sudden deafness when he complained of severe or complete hearing loss occurring instantly or progressing

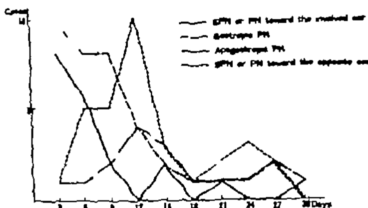


Fig 2. Incidence of the four types of nystagmus after vertiginous attack.

two weeks. In the case of SPN (or PN) toward the opposite ear the incidence gradually increased, reached a peak on the 9-12th day and receded thereafter. No specific pattern in the incidence of apogeotropic PN was found because of the small number of cases.

3. *Transition of nystagmus types in individual cases*

Based on the above described results the types of SPN and PN appear to be divided into two one which occurs in early stages of the disease and the other which develops in later stages. Further details of transition of nystagmus types were examined on each of the 31 cases (Table III).

Of the 31 cases 18 (58.1 %) showed all three or a combination of any two of the following in the order described in Table III*a*: SPN (or PN) toward the involved ear- geotropic PN and SPN (or PN) toward the opposite ear (Fig. 3). Four cases (12.9 %) showed a combination of

Table III. *Transition of nystagmus types in individual cases*

(*a*) SPN or PN toward the involved ear →	Geotropic PN	→ SPN or PN toward the opposite ear	
		+	3
			1
			8
		+	6
			18
(*b*) SPN or PN toward the involved ear →	Apogeotropic PN	→ SPN or PN toward the opposite ear	
			2
		+	2
			4
(*c*) Geotropic PN	→ SPN or PN toward the opposite ear	→ Apogeotropic PN	
			2
		+	2
			4
(*d*) SPN or PN toward the opposite ear	Apogeotropic PN	→ SPN or PN toward the involved ear	
			2
			1
			3
(*e*) Miscellaneous			2
Total			31

position The incidence of a nystagmus toward the involved ear in the supine position was higher in the cases with SPN or direction-fixed PN than in those with direction-changing PN 12 of 17 for the former group and 5 of 10 for the latter

2. Findings in the total 140 tests

Table II lists the types of nystagmus in the total of 140 tests performed on the 31 cases. The different types of nystagmus were encountered in the following order of slightly decreasing incidence geotropic (direction-changing) PN was found in 40 (28.5) of the total of 140 tests SPN or (direction-fixed) PN toward the opposite ear 36 (25 7) apogeotropic (direction-changing) PN 25 (17 9 %) and SPN or (direction fixed) PN toward the involved ear 21 (15 0 %) No nystagmus was observed in 17 tests (12.1 %) There was an unclassifiable type of direction changing PN whose direction was the same in both lateral positions.

The tests were divided into two groups according to the time of testing (Table II and Fig. 1) There were 49 tests which were performed within the first week after a vertiginous attack and 91 tests were conducted in the second week or later Fewer cases of SPN (or PN) toward the involved ear were observed in the second group

Table II Types and time of occurrence of SPN and PN

	No. of cases	During the 1st week	During the 2nd week or later
SPN or PN toward the involved ear	21	15	6
Geotropic PN	40	1	19
Apogeotropic PN	25	2	23
SPN or PN toward the opposite ear	36	9	27
Nystagmus absent	17	1	16
Unclassifiable	1	1	0

than in the first group In contrast the majority of apogeotropic PN and SPN (or PN) toward the opposite ear was found in the second group. Although cases of geotropic PN were distributed equally in both groups, a type of geotropic PN which has a nystagmus toward the involved ear in the supine position was present only in the first group (Fig. 1b)

The incidence of the above-mentioned four types of nystagmus during the 30 day period after a vertiginous attack is shown in Fig. 2 In the case of SPN (or PN) toward the involved ear as well as of geotropic PN the incidence was the highest immediately after the day of onset and decreased abruptly during the subsequent

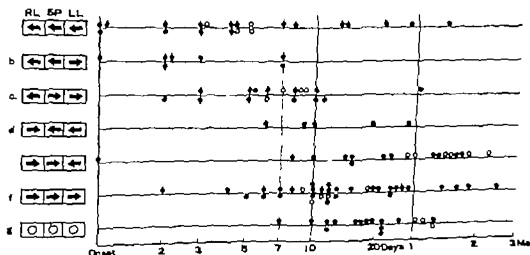


Fig 1 Findings in the total of 140 tests. The right ear was assumed to be involved in all the cases. Filled circles indicate cases with Ménière's disease or aural vertigo of unknown etiology while unfilled circles indicate cases with sudden deafness. The results of the initial testing are shown by the circles with vertical lines. *SP* supine position *RL* and *LL*, right and left side down positions.

No difference was present in the pattern of nystagmus transition between the patients with *Ménière's disease* or aural vertigo of unknown etiology both of which are thought to be caused *similarly by autonomic dysfunction* (Uemura et al., 1972), and those with sudden deafness.

COMMENTS

Changes in the features of nystagmus during the course of peripheral labyrinthine diseases especially of PN have scarcely been investigated. Gerlings (1948) described the transfer between direction-changing PN and SPN or direction-fixed PN of the patients who had otitis media or underwent ear surgery. Aschan & Stahle (1957) reported that direction-changing PN was found in 5 of the 21 cases with Ménière's disease tested during or after the attacks. In this series the transfer between direction-changing and direction-fixed PN was noted in 3 cases.

Although these findings had indicated that peripheral lesions might also cause direction-changing PN they did not clarify the relationship between the nystagmus pattern and the inner ear pathology.

The present study of the 31 cases, approximately two thirds of which started to receive follow-up examination within the first week following a vertiginous attack, demonstrated that SPN and PN could be divided into two types according to the time of occurrence: first, SPN (or PN) toward the involved ear and geotropic PN with the highest incidence immediately after the vertiginous attack; and second, SPN (or PN) toward the opposite ear and, presumably apogeotropic PN which had the peak of incidence approximately two weeks later. Furthermore, it appeared from the analysis of the test results of individual cases that SPN (or PN) toward the involved ear which is referred to as irritative nystagmus was followed by geotropic PN and SPN (or PN) toward the opposite ear referred to as paralytic or destructive nystagmus, by apogeotropic nystagmus.

Thus, the non-inflammatory inner ear diseases including Ménière's disease, aural vertigo of unknown etiology and sudden deafness were shown to have a uniform pattern in the appearance of nystagmus.

This suggests that these diseases may follow the similar course from the irritative to the paralytic process in the vestibular labyrinth. The transition from SPN (or PN) toward the opposite ear to apogeotropic PN was thought to be related to the recovery or compensatory process, because it occurred in the latest stage of the course.

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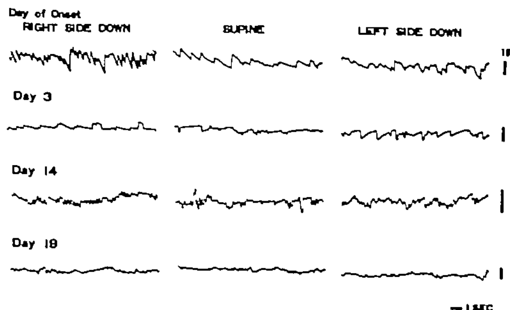


Fig 3 Ménière's disease of the right ear 40-year-old male. Horizontal eye movements were recorded binocularly with the eyes open in the dark. Upward pen deflections indicate eye movements to the right. On the day of onset nystagmus to the right was present in the supine, right and left side down positions. On the third day nystagmus when lying with the left side down was reversed to the left, indicating that this was geotropic PN Nystagmus to the left alone was present in the supine and left side down positions on the 14th day No nystagmus was revealed on the 19th day

any two of the following in the order described in Table III *b* SPN (or PN) toward the involved ear apogeotropic PN and SPN (or PN) toward the opposite ear Four other cases (12.9) showed all or two of the following in the order described in Table III *c* geotropic PN SPN (or PN) toward the opposite ear and apogeotropic PN (Fig. 4) This group can be regarded as the same as the 18 cases of the first group because they both had geotropic PN and SPN (or PN) toward the opposite ear or SPN (or PN) toward the opposite ear alone The transition from SPN (or PN) toward the involved ear to apogeotropic PN in two cases of the second groups is also included in the above-mentioned order of SPN (or PN) toward the involved ear geotropic PN SPN (or PN) toward the opposite ear and apogeotropic PN Thus 24 of 31 cases were found to have a uniform pattern of nystagmus transition after a vertiginous attack

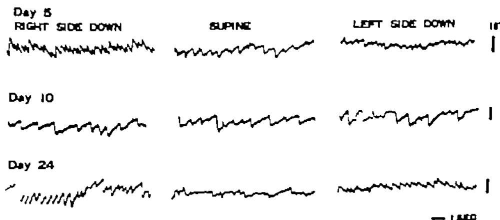


Fig 4 Sudden deafness in the right side, 1-year-old male. All the records were made under the same conditions as in Fig. 3 Geotropic PN was present on the fifth day after the onset. Nystagmus when lying with the right side dow reversed its direction to the left on the 10th day Nystagmus in the left side down position was toward the right on the 4th day indicating that this was apogeotropic PN.

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MENIERE'S DISEASE AND DIPHENIDOL

A Critical Analysis of Symptoms and Equilibrium Function Tests

T Futaki M Kitahara and M Morimoto

From the Department of Otolaryngology School of Medicine Kyoto University Shogoin, Sakyo-ku Kyoto 606 Japan

Abstract In 24 patients with Ménière's disease, chemotherapy using Diphenidol (1 1-diphenyl-4-piperidino-1-butanol hydrochloride), a non-phenothiazinic antiemetic agent, was carried out using the double-blind technique in the cross-over design. The prevalence and intensity of symptoms at the three stages were recorded every three weeks according to fixed scales which were graded vertigo, unsteadiness, tinnitus, nausea, headache, and shoulder stiffness. The hearing was measured by tone audiometry Equilibrium function tests were also performed every three weeks and these included the electronystagmographical procedure to determine caloric response and the ARG Tilt tests. Both symptoms and the results of equilibrium function tests, showed a higher incidence of improvement during the period of Diphenidol administration than during that of placebo. The difference was statistically significant with respect to vertigo, dizziness or unsteadiness, and general condition subjectively as well as caloric response and ARG Tilt tests. The Diphenidol effect consisted of an improvement of imbalance, both in the peripheral and in the central vestibular system through its neural and circulatory action. Only 8 of the patients dropped out and no side effects were observed in this series. Both the feasibility of the graded symptom scales and the utility of each parameter obtained from the equilibrium function tests are discussed in connection with testing of the drug in various stages of the disease.

Ménière's disease is presently diagnosed by clinical symptoms such as episodic vertigo tinnitus and loss of hearing. In addition to the characteristic clinical features, the disease has attracted considerable interest because of its usually recurrent or chronic nature The unpleasant and partly incapacitating nature of the symptoms has been a strong incentive in the search for suitable forms of therapy Not all patients with Ménière's disease necessarily require surgery Rather this treatment should be restricted to those who complain of incapacitating, frequent longlasting, severe attacks of vertigo Conservative treatment should be adequate for patients with mild cases of Ménière's.

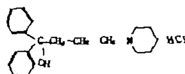
Chemotherapy for Ménière's includes vasodilators, histaminics, psychotropics, vestibular suppressives, salt and water restriction, diuretics and steroids

A most judicious prescription of diuretics and steroids is necessary as side effects such as decreased potassium levels in the serum, ulceration in the alimentary canal and the moon face are often observed Diuretic and steroid chemotherapy *is therefore not suitable for long term* administration but should be prescribed for cases of exacerbation of labyrinthine disorders in chronic cases.

Certain vasodilators and histaminics have been prescribed and reported as effective in the preventive treatment of Ménière's. Vestibular suppressives also may be employed during the irritative stage of Ménière's

To eliminate stress factors which often enhance the symptoms, sedatives or tranquillizers may also be employed Despite these various prescriptions, no specific agent which is both safe and effective has been formulated Taking the following factors into consideration diphenidol was proposed for the treatment of Ménière's disease for the following reasons

(1) Diphenidol is an antiemetic agent with a non phenothiazinic chemical structure It was



1,1-diphenyl-4-piperidino-1-butanol hydrochloride

Fig. 1. Chemical structure of diphenidol.

synthesized by Leonard *et* al. in 1966 (Fig. 1). It can block apomorphine-induced emesis as rapidly as chlorpromazine and has minimal depressant action on the C.N.S.

(2) Electrophysiologically the excessive discharge at the vestibular nuclei was depressed by the i.v. administration of diphenidol to cats (Matsuoka, 1972).

(3) This agent successfully diminishes experimentally induced nystagmus (Matsunaga, 1972).

(4) The velocity of blood flow in the vertebral artery is selectively and significantly increased on the side of the affected labyrinth (Shiraishi, 1971).

(5) This agent has been reported to be effective for patients with vertigo (Smoot, 1965; Rowan, 1968; Matsunaga et al., 1972) and motion sickness (Berry & McCornell, 1965).

(6) From the results of studies as well as clinical experience there appears to be a considerable margin between the therapeutic dose and that which produces undesirable side effects.

Encouraged by these favourable properties of diphenidol, a controlled clinical trial was carried out on 24 patients with typical and atypical Ménière's disease. One of the main objectives was to investigate whether or not the efficacy of the drug as the result of parenteral administration could be elicited over a period of 3 weeks of oral administration and, in addition, to determine the relationship between changes in subjective symptoms and objective findings such as

Table I. *Grading of symptoms in Ménière's disease according to criteria set for the present study*

Tinnitus	Vertigo	Dizziness and unsteadiness	Nausea
0 None	None	None	None
0.5 Slight, periodic			
1.0 Slight, continuous or moderate, periodic	Seldom or frequent, immediately transient rotatory vertigo or severer but brief (30 min), max. 2/mo.	Unreliable function in situations requiring balance. Rapidly transient, slight rotatory vertigo on quick head movements	Accompanied by dizziness
1.5 Continuous, fluctuating from slight to moderate			
2.0 Continuous, moderate or fluctuating from slight to severe. Intermittent, severe	Intense but brief attacks, 2/mo. Intense, lengthy (30 min) often with vomiting, max. 2/mo.	Short periods (30 % prevalence) of balance disturbance	Occasionally accompanied by dizziness
2.5 Continuous, fluctuating from moderate to severe			Continuously present
3.0 Continuous, severe	Intense, lengthy 2/mo	Longer periods (>30 prevalence) of balance disturbance	

Audible only in quiet environment.
Audible in ordinarily noisy environment but divertible, i.e., not observed when attention focused on work, etc.
Constantly noticed in all ordinary acoustic environments and even when concentrating on work, etc.

equilibrium function tests. Assessement of the drug for side effects and a determination of the reliability of the test was also considered, as the cross-over method involved necessitated a trial of 6 weeks.

METHODS

The following distinctions, criteria and procedure were applied during the entire series.

At the start of the trial, patients who subjectively had a complete triad of symptoms including idiopathic vertigo tinnitus and hearing loss of the perceptive type were diagnosed as typical Ménière s disease and those with episodic vertigo without or at least unaware of cochlear signs were regarded as atypical Ménière s.

Since initial symptoms of Ménière s disease are so varied and since many months may pass before the syndrome is complete in the former the diagnosis is more uncertain in the latter in which the initial symptoms are vestibular onl Patients both with labyrinthine disease of know etiology and with extralabyrinthine lesions whic could cause the attacks, were carefully elimi ated from the Ménière s disease grouping. Th 24 patients with Ménière s were selected for controlled clinical evaluation of diphenidol. Th symptoms of Ménière s disease were graded an recorded according to the scales described i Table I with reference to the report by Kloc holf & Lindblom in 1967 covering hydrochlor thiazide The scales consisted of a numeric grading of the symptoms, with respect to inte sity and prevalence The evaluation was mad three times i e at the beginning of trial, weeks after the first medication and a further weeks after the second medication, on the bas of verbal statements by the patients themselve A particular doctor was assigned to each patien in order that variation by multiple inquirer should not occur

The design for the trial was a cross-ove method (Fig. 2) lasting for 6 weeks. One bott of tablets was allotted to each patient. Content were either diphenidol or placebo of identica appearance (lactose) and each bottle was labelle with its own code number randomised by th controller The patients were instructed t take 1 tablet three times a day after meals, an each bottle was carefully checked 3 weeks later One active tablet contained 25 mg of diphenidol, i e 75 mg a day The code was not broken unti the study was completed These periods wer preceded by a week of washing-out medication No other chemical agent was ingested throughout the trial.

Side effects were carefully checked at each end point of medication.

Audiometry Pure tone audiometry was performed three times, using the Rion-AA 34 The meaning of the hearing-loss figures, i.e $a+2b+c/4$ at the frequencies 500 (a) 1 000 (b) and 2 000 (c) Hz was taken as representative of each audiogram

Equilibrium function tests Equilibrium function tests were also performed every 3 weeks and these included the electronystagmographical

Headache	Stiffness in the shoulders
None	None
Mild, occasional	
Mild, continuous or moderate occasional	Mild, or moderate together with other symptoms
Continuous, fluctuating from mild to moderate	
Continuous, fluctuating from moderate or mild to intense. Intermittently severe	Continuous, moderate
Continuous, fluctuating from moderate to intense	
Continuous, intense	Continuous, intense

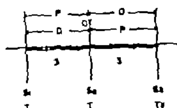


Fig. 2. Design of a 6-week trial using the cross-over technique. *P*, Placebo; *D*, diphenidol; *S*, symptom; *T*, tests of equilibrium function.

procedures as follows: (1) ARG-Tilt test and (2) the caloric test.

Recording no. 1 was carried out simultaneously with ENG, using a strain-gauge-type amplifier (Kyowa Denki Ltd.) conducted from the accelero-meter attached to the forehead that was set at a speed of 1 /sec by electric motor driven goniometer (manufactured by Matsui). Recording no. 2 was carried out by three channelled d.c. ENG (San-ei Sokki Ltd.).

The caloric tests were carried out with the patient in a supine position and using 50 cc of water at 30°C. Ice-cold water was used in cases where no reaction was obtained with this stimulus. Immediately after the irrigation, the room was darkened.

Statistical analysis. Concerning subjective symptoms, the sequential analysis (Armitage) was employed for both global comparative judgement and for each symptom. As to the objective findings, i.e. the pure tone audiometry and the equilibrium function tests, these were analysed using T tests. In addition, some were illustrated in the diagram of the sequential analysis.

RESULTS

1. Symptoms

An example of the accommodated value of each subjective symptom based on the judgement criteria is shown in Table II (with the 2nd sequence patient of Code number 73). Since the sum of (S_1-S_4) of each symptom was larger than that of (S_1-S_3), the second bottle of the drug was estimated effective or as the real drug and (+) was written. In the bottom row placebo (*P*) and diphenidol (*D*) were the order of the administration shown by the controller after breaking the seal for blindness with code number 73 at the completion of the entire series of patients. This global comparative judgement is an example of "win" since the order of (−) and (+) were in accord with that of *P* and *D* respectively.

The judging of the 24 patients according to symptoms is shown in Table III. When the results in Table III were graphically analysed by the sequential technique of Armitage, the curve crossed the limit line at the sixth case (Fig. 3). It was therefore concluded that diphenidol was significantly more effective in the global comparative judgement of subjective symptoms than was placebo ($\alpha=0.05$, $1-\beta=0.95$ and $\theta=0.85$).

With regard to each symptom the sequential analysis was also carried out. Fig. 4 shows the results related to each symptom. It was also concluded that diphenidol was more significantly effective than placebo in vertigo (*V*) and dizziness (*D*) or unsteadiness ($\alpha=0.05$, $1-\beta=0.95$ and $\theta=0.85$). The others remained in the lattice, i.e. more cases should be examined.

2. Pure tone audiometry and equilibrium function tests

Yielded values with diphenidol and placebo concerning the parameter Objective Findings are shown in Table IV.

Table II. *Sample of the judgement table of the symptoms in the 2nd sequence of patients*

S_1, Symptoms before trial; S_4, Symptoms after first medication; S_s, The ones after second medication; *T*, Tinnitus; *V*, Vertigo; *D*, Dizziness or unsteadiness; *N*, Nausea; *H*, Headache; *S*, Shoulder stiffness; *P*, Placebo; *D*, Diphenidol.

No. 2	Affected R						
S_1–S_4	S_1		S_4		S_4		S_1–S_4
0	*T*	0	*T*	0	*T*	0	0
0	*V*	1.0	*V*	1.0	*V*	1.0	0
0	*D*	1.0	*D*	1.0	*D*	0	1.0
0	*N*	1.0	*N*	1.0	*N*	0	1.0
1.5	*H*	0.5	*H*	2.0	*H*	0.5	1.5
1.0	*S*	1.0	*S*	2.0	*S*	0	—0
—5	−				+		5.5
Code No. (73)	*P*				*D*		
P–*D*	Judgement (in)						

Table III *Symptomatic results of administration of diphenidol or placebo in 24 patients with Ménière's*
Mt = typical Ménière's disease, Ma = atypical Ménière's disease

Patient no.	Age	Sex	Diagnosis	Administration order		Total of (S_1–S_2)	Total of (S_1 S_2)	Judgement of effectiveness 1st drug	2nd drug	Side effects and drop-outs
1	21	F	Mt	*D*	*P*	0	−3 0	+	−	
	_8	M	Mt	*P*	*D*	_5	5.5	−	+	
3	38	F	Mt	*D*	*P*	3 5	3 0	+	−	
4	45	M	Ma	*P*	*D*	−1 0	−0.5	−	+	
5	39	F	Ma	*P*	*D*	0	0.5	−	+	
6	58	M	Mt	*P*	*D*	−0.5	0	−	+	Abdominal disorders with placebo
7	45	M	Mt	*P*	*D*					Drop-out
8	43	F	Mt	*D*	*P*	−1 0	−_5	+	−	
9	37	M	Ma	*D*	*P*	−0.5	−0.5	Draw		
10	51	F	Ma	*D*	*P*	−0.5	−1 0	+	−	
11	_8	F	Mt	*P*	*D*	−1 0	2.5	−	+	
1	47	F	Mt	*P*	*D*	−_5	1 0	−	+	
13	56	F	Ma	*D*	*P*	0	0	Draw		
14	33	F	Mt	*D*	*P*	0.5	0.5	+	−	
15	65	M	Ma	*P*	*D*	1 0	1 0	Draw		
16	48	F	Mt	*D*	*P*	2.5	_5	+	−	
17	68	M	Ma	*P*	*D*	1 0				Drop-out
18	31	F	Mt	*D*	*P*	−4 0	1 0	−	+	
19	56	M	Ma	*P*	*D*	−1 0	0	−	+	
20	_6	M	Ma	*D*	*P*	3.5	3.5	−	+	
1	^0	M	Ma	*P*	*D*	−2.0	1.5	−	+	
22	53	F	Ma	*P*	*D*	_0	4 5	−	+	
23	50	F	Mt	*P*	*D*	_0	_0	−	+	
4	41	F	Mt	*P*	*D*	1.5	6.0	−	+	

Hearing shift The affected sides were regarded in atypical Ménière's disease at the ipsilateral side of lower caloric response Two cases were excluded because of equal responses Hearing shifts in the affected ears were compared in 20 patients with the result that diphenidol was found significantly ineffective in cases of hearing loss

ARG Tilt test Utilizing the ARG Tilt test, precise measurements of the labyrinthine righting reflex could be observed in three dynamic aspects, represented by the parameters shown in Fig. 5 (1) *A* Sum of angles of falling on tilting to the right and left (at a tilting speed of 1 /sec). (2) *H* Sum of angles of head inclination. (3) *U* Sum of angles of unrest head swaying. An in-

Table IV *Results in pure tone audiometry and equilibrium function tests*

	N	Mean	S.D	*T*	Significance level
Hearing shift (dB)	^0	1 45	6.59	1.035 2.09	
ARG Tilt test					
A *D*–*P* (Degree)	22	2.1	8.3	1 19 < 2.07	
H *P* *D* (*G*)	_2	0 106	0.161	3 09 > _07	(0.05)
U *P* *D* (*G*)	22	0.107	0.151	3.32 2.07	(0.05)
Caloric response					
Maximum velocity *P* *D*	1	0.120	0._46	2._3 > 2.08	(0.05)
Maximum intensity *P* *D*	21	0.155	0.308	2.35 > 2.08	(0 05)
Frequency *P* *D*	20	−0.3	11 8	0.12 < _09	

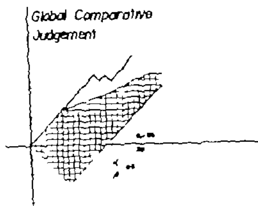


Fig. 3. Sequential analysis of global comparative judgement. N Sequential number reaching significant level. (0.05, 1 β 0.95, θ = 0.85).

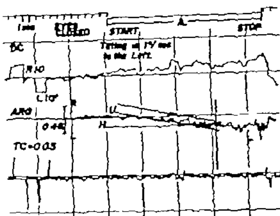


Fig. 5. A recording of ARG-Tilt test. A, Angle of falling on tilting; H, head inclination; U, degree of unrest head swaying.

crease in A and a decrease in H and U can be interpreted as an improvement in the labyrinthine righting reflex (Kitahara, 1965). The results after administration of diphenidol showed a significant decrease in both head inclination and unrest head swaying at the 0.05 level, but an increase in the angles of falling was not significant, as seen in Table IV.

Total judgment of ARG-Tilt test, providing a win was recorded in a case with more than two parameters of A, H and U effective with diphenidol, was shown in sequential analysis (Fig. 6). This curve crossed the limit line at the ninth case. Thus the results were significant ($\alpha = 0.05$, $1-\beta = 0.95$, $\theta = 0.85$). Accordingly it was concluded that diphenidol, rather than the placebo caused significant improvement in the labyrinthine righting reflex for the maintenance of body equilibrium.

Caloric responses. As parameters of caloric nystagmus the following were used (1) a ratio of differences between the right and left in maximum velocity of the slow component. $(R-L)/(R+L)$ (Mv) (2) a ratio of differences between the right and left in maximum intensity (Stahle, 1958). $(R-L)/(R+L)$ (MI) and (3) sum of the right and left maximum frequency of nystagmus for 10 sec. As for the maximum velocity (Mv), t-test showed that diphenidol caused a decrease in the right-left differences of caloric response at the 0.05 level.

An illustration of sequential analysis of Mv

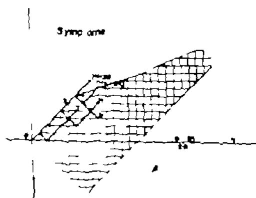


Fig. 4. Sequential analysis of each symptom. Abbreviations as in Table II and Fig. 1.

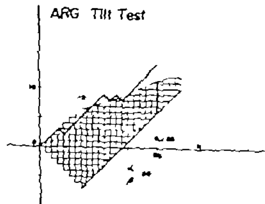


Fig. 6. Sequential analysis of ARG-Tilt test. Abbreviations as in Fig. 1.

Table III *Symptomatic results of administration of diphenidol or placebo in 24 patients with Ménière s*
Mt = typical Ménière s disease, Ma = atypical Ménière s disease

Patient no.	Age	Sex	Diagnosis	Adminis-tration order		Total of (S_1–S_4)	Total of (S S_4)	Judgement of effectiveness 1st drug	2nd drug	Side effects and drop-outs
1	21	F	Mt	D	P	0	−3 0	+	−	
2	28	M	Mt	P	D	2.5	5 5	−	+	
3	38	F	Mt	D	P	3.5	3 0	+	−	
4	45	M	Ma	P	D	−1 0	−0.5	−	+	
5	39	F	Ma	P	D	0	0.5	−	+	
6	58	M	Mt	P	D	−0.5	0	−	+	Abdominal disorders with placebo
7	45	M	Mt	P	D					Drop-out
8	43	F	Mt	D	P	−1 0	−2.5	+	−	
9	37	M	Ma	D	P	−0.5	−0.5	Draw		
10	51	F	Ma	D	P	−0.5	−1 0	+	−	
11	8	F	Mt	P	D	−1 0	2.5	−	+	
1	47	F	Mt	P	D	−2.5	1 0	−	+	
13	56	F	Ma	D	P	0	0	Draw		
14	33	F	Mt	D	P	0.5	0.5	+	−	
15	65	M	Ma	P	D	1 0	1 0	Draw		
16	48	F	Mt	D	P	2.5	5	+		
17	68	M	Ma	P	D	1 0				Drop-out
18	31	F	Mt	D	P	−4 0	1 0	−	+	
19	56	M	Ma	P	D	−1.0	0	−	+	
20	26	M	Ma	D	P	3.5	3.5	−	+	
21	20	M	Ma	P	D	−2.0	1.5	−	+	
22	53	F	Ma	P	D	2.0	4.5	−	+	
3	50	F	Mt	P	D	2.0	0	−	+	
24	41	F	Mt	P	D	1.5	6.0	−	+	

Hearing shift The affected sides were regarded in atypical Ménière s disease at the ipsi lateral side of lower caloric response Two cases were excluded because of equal responses. Hear ing shifts in the affected ears were compared in 20 patients with the result that diphenidol was found significantly ineffective in cases of hearing loss

ARG-Tilt test Utilizing the ARG Tilt test, precise measurements of the labyrinthine right ing reflex could be observed in three dynamic aspects, represented by the parameters shown in Fig. 5 (1) *A* Sum of angles of falling on tilting to the right and left (at a tilting speed of 1 /sec). (2) *H* Sum of angles of head inclination. (3) *U* Sum of angles of unrest head swaying. An in-

Table IV *Results in pure tone audiometry and equilibrium function tests*

	N	Mean	S.D	T	Significance level
Hearing shift (dB)	20	1 45	6.59	1.035 < 2.09	
ARG Tilt test					
A D–P (Degree)	22	−2.1	8.3	1 19 < 2.07	
H P D (G)	22	0.106	0.161	3 09 > 2.07	(0.05)
U P–D (G)	22	0 107	0.151	3.32 2.07	(0.05)
Caloric response					
Maximum velocity *P–D*	21	0.120	0.246	2.23 > 2.08	(0.05)
Maximum intensity *P–D*	21	0.155	0.308	2.35 > 2.08	(0.05)
Frequency *P D*	20	−0.3	11 8	0.12 < 2.09	

gradation of symptoms was thus employed d the antivertiginous effect of diphenidol oved to be more dominant than the antiemetic e, as well as the suppressive effect in cochlear mptoms such as tinnitus. This dominance ight be responsible for the improvement in the neral condition of the symptom complex.

Although the mechanism and site of action of iphenidol may to some degree have been ucidated, the indices of choice in objective indings should be given careful consideration. Pure tone audiometry and equilibrium function tests including electronystagmographical procedures were chosen because these are the well established methods in investigation of Ménière's disease. Regarding objective findings, there is no mention of the efficacy of diphenidol in the literature, except for Shiraishi's report concerning the blood flow in the vertebral artery as quoted earlier. Matsunaga reported that a discrepancy exists between the symptomatic efficacy and the results of audiometry and equilibrium function tests including investigation of spontaneous and positional nystagmus with Frenzel's glass, stepping tests and vertical writing tests. Electronystagmographical procedures employed in this study are considered to result in a higher detectability rate than with the above mentioned screening tests. The audiometric results in the present study parallel those of Smoot & Matsunaga in that no change was detected in pure tone audiometry. It has been reported that hearing improvement in the affected labyrinth in Ménière's disease is brought about by some diuretics, i.e. hydrochlorothiazide (Klockhoff & Lindblom, 1967) glycerol (Klockhoff & Lindblom, 1966) and furosemid (Futaki, Kitahara & Morimoto 1975). These authors assumed that a hearing shift was caused by temporary reduction of endolymphatic hydrops as a result of systemic diuresis. Compared with the action of diuretics, that of diphenidol on the cochlea appears to be more indirect. In fact, as another cochlear symptom, tinnitus remained in the lattice (Fig. 4).

Regarding equilibrium function tests, two types of investigation were performed, mainly in connection with the two anatomical neural pathways, i.e. the vestibulo-spinal and the vestibulo-oculomotor tract, both including reticular connections. For investigating the natural reactions of the labyrinth which maintains the equilibrium of the body the examination related to the labyrinthine righting reflex, i.e. ARG-Tilt test (Kitahara, 1965) was carried out. He reported that in more than 90% of 46 patients with Ménière's disease, the imperfect occurrence of the head righting reflex was revealed, and that in Ménière's disease the results of the tilt test were closely related to those of Hallpike's caloric test.

As for the results of ARG-Tilt test in this study it was clearly demonstrated that diphenidol caused a significant improvement of the labyrinthine righting reflex required to maintain body equilibrium. As quoted above, the improvement shown by the results of ARG-Tilt tests was also closely related to the results obtained in caloric responses which revealed a significant reduction of imbalance of labyrinthine function during the period of diphenidol administration.

The caloric test has been recognized as one of the most reliable tests in determining which ear is impaired in various vestibular examinations (Cawthorne et al., 1942, Stahle & Bergmann, 1967). Therefore, the improvement in caloric response is considered as essential for treatment of Ménière's disease. Since the chief aim of therapy is to produce a homeostatic state, either medically or surgically it is desirable that the pharmacokinetics of a drug should act selectively with a balanced state as a result.

Both the damping of the excessive discharge at the vestibular nuclei in cats (Matsuoka, 1972) and the selective increase in blood flow in the vertebral artery on the side of the affected labyrinth in man (Shiraishi et al., 1971) on injecting with diphenidol, may be regarded as being related to the causal mechanism of the improved objective findings after oral administration of diphenidol for 3 weeks (75 mg a day).

Finally it is also emphasized that side effects were nil and that only 2 (8%) patients dropped out"

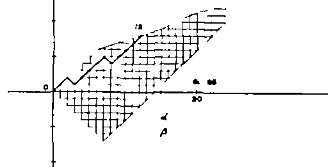


Fig 7 Sequential analysis of caloric tests in maximum velocity

is shown in Fig. 7 The curve crossed the limit line at the twelfth case which indicates that this drug significantly reduces the imbalance of the labyrinthine functions ($\alpha = 0.05$ $1-\beta = 0.95$ $\theta = 0.85$)

As for the maximum intensity the *t* test showed at the 0.05 level that diphenidol significantly decreases the right-left differences, in comparison with placebo as was also seen with sequential analysis at $n = 12$ ($\alpha = 0.05$ $1-\beta = 0.95$ $\theta = 0.85$) (Fig. 8)

As for the maximum frequency of nystagmus for 10 sec, neither *t* test nor sequential analysis showed any significant result. As this drug significantly decreased the imbalance of excitability of the labyrinth, states close to that of equilibrium were realized.

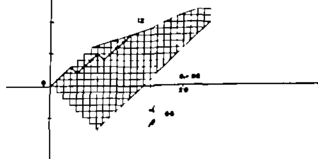


Fig 8 Sequential analysis of caloric tests in maximum intensity

DISCUSSION

In this controlled study both the symptoms and the results of equilibrium function tests showed a higher incidence of improvement during the period of diphenidol administration than during that of placebo The difference was statistically significant with respect to vertigo dizziness or unsteadiness and general condition subjectively as well as caloric response and ARG-Tilt test.

Smoot reported in 1965 from his open trial with oral administration of diphenidol that the drug was safe and effective in 8 patients with non-operative labyrinthine disturbances, including 6 Ménière s patients and in 14 patients with post-operative labyrinthine disorders chiefly caused by stapedectomy There is a distinct difference between unavoidable postoperative vertigo and episodic vertigo of Ménière s disease regarding occurrence and duration. Also since the vertigo of labyrinthitis and sudden deafness is more clear cut than that of Ménière s disease, the design of the clinical trials should be carefully determined, as the disease is usually recurrent and of a chronic nature Such being the case, the cross-over method to detect intra individual differences was chosen for this study

The symptomatic results of the present study are in agreement with two controlled studies by Rowan (1968) and Matsunaga et al. (1972). These two reports included vertiginous patients with various etiologies, such as central vertigo as a result of arteriosclerosis, and traumatic vertigo Due to insufficient stratification it was only estimated that diphenidol appeared to be more effective in peripheral than in central vertigo and firm conclusions about the drug s relative efficacy were not drawn.

The characteristic clinical features of Ménière s disease are not only related to the varied presence of the triad but also to the existence of accompanying symptoms such as nausea headache and shoulder stiffness. In order to estimate the efficacy of the drug in this disease it is important that two aspects must be considered, the variation in each symptom and the general condition of the symptom complex. The numeri-

al gradation of symptoms was thus employed and the antivertiginous effect of diphenidol proved to be more dominant than the antiemetic one, as well as the suppressive effect in cochlear symptoms such as tinnitus. This dominance might be responsible for the improvement in the general condition of the symptom complex.

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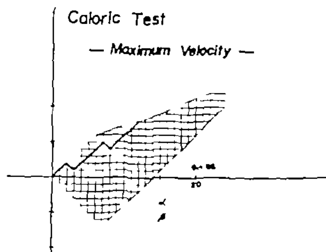


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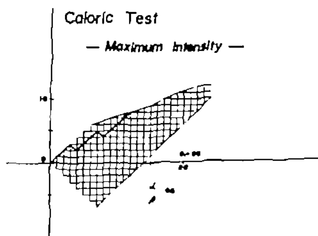


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Finally it is also emphasised that side effects were nil and that only 2 (8%) patients "dropped out".

SUMMARY

A double blind trial to evaluate a new agent, non phenothiazinic antiemetic-diphenidol, synthesized in 1966 was carried out on 24 patients with confirmed Ménière s disease. Clinical and statistical evaluation of the results showed that diphenidol is indeed effective for subjective symptoms and positive results were evident in equilibrium function tests. There were no apparent side effects. Difficulties related to conducting anti-vertiginous tests in chronic Ménière s are discussed.

ZUSAMMENFASSUNG

Ein Double Blind Versuch zur Abschätzung eines neuen Agens, nonphenothiazinischen Antiemetik Diphenidols, das 1966 synthesiert wurde, wurde an 24 Patienten mit chronischer Ménièrescher Krankheit durchgeführt.

Klinische und statistische Auswertung der Ergebnisse zeigt dass das Diphenidol deutlich auf die subjektiven Symptome einwirkt. Das positive Resultat ist durch den Gleichgewichtstest klar geworden.

Es gibt keine offensichtliche Nebenwirkungen. Schwierigkeiten des Gegenschwindel-Tests bei chronischer Ménièrescher Krankheit wurden diskutiert.

ACKNOWLEDGEMENTS

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LE TRAITEMENT DU « VERTIGE » POST TRAUMATIQUE ACCOMPAGNÉ D ATAXIE CÉRÉBELLEUSE FRUSTE

Efficacité de la procaïnisation des muscles érecteurs lombaires

Nobuya Ushio

Service d'oto-rhino-laryngologie Ecole de Médecine, Université de Tokushima, Japon et Centre Hospitalier Sainte-Anne Laboratoire de Stabilométrie

. est vérifié expérimentalement sur des animaux et des mannequins que le tissu et les éléments vasculaires, articulaires et osseux cervicaux subissent une lésion fonctionnelle ou organique lorsque l'axe du corps d'un sujet est soumis à une hyperextension ou une hyperflexion. Il est bien connu que parmi tous les tissus et les éléments anatomiques cervicaux le propriocepteur situé dans les tissus de soutien mous (les muscles), les organes de Ruffini dans les ligaments, la capsule et l'articulation, les organes de Golgi dans les tendons, les nerfs sympathiques, et l'artère vertébrale, peuvent être concernés lors de l'apparition du vertige cervical. Par conséquent on a fait depuis longtemps des recherches sur les rôles que jouent au moment de l'apparition du « vertige » cervical l'anomalie fonctionnelle et la lésion organique de ces tissus et de ces organes. Il y a déjà plusieurs théories sur ce problème dont voici les principales (1) l'hyperfonctionnement du grand sympathique cervical, (2) le dysfonctionnement du reflexe cervical, (3) la circulation insuffisante de l'artère vertébrale.

Nous avons aussi indiqué que l'hypertonicité des tissus de soutien mous cervicaux, est une des causes principales de l'apparition du vertige cervical. Or en observant des cas de « vertige » chez des traumatisés cervicaux, nous avons remarqué qu il y avait de nombreux cas accompagnés de douleurs lombaires et que ces derniers se rencontrent en proportion directe avec le vertige (Ushio 1970). Dans ces cas, la plupart s accompagnent en même temps d anomalies fonctionnelles tronculaires et cérébelleuses. Ceci nous a conduit à penser que les tissus de soutien mous lombaires, le tronc et le cervelet, avaient un rapport les uns avec les autres comme une détente et une cible, et se rattachaient à l'apparition du « vertige » cervical. Par conséquent, l'essentiel du traitement du vertige dans ces cas, consiste, comme nous l'avons indiqué dans le cas du vertige cervical, d une part à la correction de l'hypertonicité des tissus de soutien mous lombaires et d autre part au rétablissement de fonctionnement du système nerveux central tels que le tronc et le cervelet.

En tant que traitement pour rétablir le fonctionnement du tronc et pour faire disparaître le vertige, nous avons souvent signalé qu'il est efficace de donner des médicaments agissant sur le fonctionnement du tronc, c est à dire, par exemple la Centrophénoxine (Lucidril), CDP-choline (Nicholin) (Hinoki et al., 1967 Ushio et al., 1970). Mais jusqu ici, nous n avons pas encore perfectionné le traitement pour le contrôle efficace des symptômes cérébelleux frustes pour accélérer l'amélioration du vertige.

Dans un article antérieur j ai montré que dans les cas des traumatisés cervicaux accompagnés d'une part de troubles non définis comme des douleurs lombaires qui peuvent être considérées

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comme l hypertonicité des tissus de soutien mous lombaires et d autre part de symptômes cérébelleux, il y en a un certain nombre dans lesquels la fonction d équilibre est améliorée par la fixation des lombes avec un corset (l examen de la fonction d équilibre se normalise) et de plus le symptôme cérébelleux fruste disparait. L examen de la fonction cérébelleuse au niveau des membres supérieurs épreuve des index, de l index nez, des marionnettes se normalise.

J ai dit en présentant les cas examinés que chez ces patients le traitement pour améliorer l'hypertonicité des tissus de soutien mous lombaires peut faire disparaître le symptôme cérébelleux et par conséquent peut être aussi un traitement du « vertige » La procaïnisation dans la partie douloureuse des lombes, est un des traitements, comme je l ai remarqué, qui peut agir d une façon efficace (Ushio 1970 1971)

Dans cet article je voudrais expliquer des cas examinés de ce point de vue, et ajouter certaines remarques

EXAMENS CLINIQUES ET THERAPEUTIQUE

1 *Sujets examinés*

J ai pu observer 28 cas de « vertiges » traumatiques accompagnés de signes cérébelleux ataxiques frustes, dans lesquels le sujet se plaignait de douleurs (élancement) dans la région lombaire Sur ces 28 cas, il y a 4 cas chez lesquels j ai pu traiter de manière répétée le patient suivant la méthode présentée et expliquée ci-dessous et suivre l évolution pendant un temps relativement long.

2 *Procédé thérapeutique de procaïnisation des muscles érecteurs lombaires*

On procède à 2 reprises à une injection de 7 5 à 10,0 cc de solution à 1 % de procaïne (additionée de 2 mg de Rinderon steroïd) dans les muscles érecteurs lombaires du côté douloureux à la hauteur de L3 et L4 et à 3 ou 4 cm de profondeur de telle sorte que le volume total de la solution injectée soit de 15 à 20 cc.

3 *Tests utilisé et leurs critères*

A *Pour examiner la fonction d'équilibre J'ai choisi les tests suivants*

1 Tests des réflexes d orthostatisme il y en deux l'un est le test de Romberg et l'autre le test de Mann. Dans les deux tests j ai utilisé un accéléromètre placé sur la tête du sujet pour enregistrer les oscillations corporelles, de telle sorte que soient objectivés et mesurés ces résultats.

2. Test du nystagmus spontané et test du *nystagmus de position.*

3 Test du piétinement de Fukuda, au cours duquel on demande au sujet de faire 100 pas en piétinant sur place.

4 Test du nystagmus optocinétique, employant *un stimulateur optocinétique de type Jung* (modifié) qui projette à raison d une fois/sec., des raies verticales de lumière qui se déplacent, à la vitesse de 0 (vitesse minimale) à 180°/sec. (vitesse maximale) de droite à gauche ou de gauche à droite

En outre nous avons effectué sur tous les sujets à l occasion de la première visite d autres examens pour mieux connaitre la fonction d équilibre Epreuve calorique rotatoire, de pôrsuite et test d écriture

B *Pour examiner l'ataxie cérébelleuse fruste on utilise les test suivants*

1 Epreuve des index
2. Epreuve de l index nez
3 Epreuve des marionnettes
4 Epreuve du genou talon
5 Réflexe H examen de la courbe de fréquence du pourcentage de diminution faite d après la méthode proposée par Ioku (Ioku 1969)

Dans les tests épreuve des index épreuve de l index nez et épreuve des marionnettes, l évolution de l'état ataxique aprés le traitement sera suivie par l augmentation ou la diminution du nombre d erreurs sur dix essais et on considére comme significatif le changement de ce nombre de plus ou moins 3 Dans le test épreuve des martionnettes, ne sera considéré comme signifi-

catif que le changement visible dans l'habileté des mouvements de prosupination.

4. *Résultats du traitement*

Comme il est indiqué ci-dessus, j'ai procédé à l'injection de procaïne dans la partie douloureuse des lombes des 28 sujets souffrant de « vertiges » traumatiques accompagnés de signes d'ataxie cérébelleuse observés aux membres supérieurs et se plaignant de douleurs *lombaires* exclusivement, à prédominance unilatérale, pour observer objectivement leur évolution au moyen des tests signalés précédemment. Sur ces 28 cas, il y en a 19 où la procaïnisation s'est montrée efficace à la première injection mais dont l'évolution n'a pu être suffisamment suivie, il y en a aussi 5 où le *traitement* par la *procaïnisation a été* abandonné à la suite de la première injection dont l'effet n'était pas satisfaisant.

Sur les 4 cas qui restent, 3 ont permis le traitement par la procaïnisation lombaire pendant un temps assez long pour observer son effet d'une manière satisfaisante et l'autre cas m'a donné une occasion d'observer l'évolution d'un sujet traité d'abord par la procaïnisation et ensuite par la traction lombaire.

Voici maintenant la description détaillée de chaque cas.

Cas 1. H.N., ♀, 39 ans, traumatisme cervical. Le sujet a eu un accident de voiture, celle-ci a été heurtée à un croisement par derrière, à l'arrêt, et la patiente a reçu à la tête un choc dont elle ne s'est pas rendu compte malgré sa *conscience restée intacte* au moment de l'accident. *Elle se plaint d'une sensation de « vertige »*. Elle avait dès le lendemain de l'accident mal au cou et des nausées et environ dix jours après le choc sont apparus la sensation de « vertige » (ou de titubation), la douleur lombaire droite, le mal *à tête et la sensation de tête* lourde. L'ortopédiste et l'ophtalmologiste auprès de qui notre patiente avait consulté n'avaient pas relevé de symptômes de quelque importance.

A. Résultats des examens d'équilibre lors de la première visite

1. Examens des réflexes d'orthostatisme.

Test de Romberg : oscillations avec les yeux ouverts et renversement vers l'arrière les yeux fermés.

Test de Mann : tendance à tomber en arrière avec les yeux ouverts et *fermés*.

2. Test du nystagmus spontané et du nystagmus de position : absence de nystagmus, présence de petits mouvements oculaires horizontaux, rapides et lents, observés la tête en position normale aussi bien qu'inclinée dans toutes les directions.

3. Test d'écriture de Fukuda : 5 lettres sont tracées verticalement 3 fois de suite les yeux bandés, l'écriture est inclinée vers la droite de 9° malgré cela aucun *signe ataxique*, comme par exemple le tremblement de la main, n'y était observé.

4. Test du piétinement de Fukuda : notre patiente a montré une déviation dont voici les caractéristiques : distance 140 cm, angle de déviation 45° et angle de rotation du corps 45°. Elle s'accompagnait de chancellement (Démarche de l'ours).

5. Test du nystagmus rotatoire de Bárány et test calorique : le résultat obtenu dans ces tests ne donne pas de différence droite-gauche dans l'excitabilité labyrinthique.

6. Test du nystagmus optocinétique : le sujet a reçu *les stimuli* optocinétiques. *La réaction* du système oculaire de l'examinée à l'égard de ces derniers était normale, le nystagmus vers la droite aussi bien que vers la gauche *se produisant* vivement dès que les stimuli étaient donnés.

7. Test de poursuite d'un objet en mouvement : les yeux, l'un aussi bien que l'autre, pouvaient *poursuivre régulièrement* l'objet en mouvement.

8. Examen de l'équilibre sous l'effet de l'adrénaline.

L'écriture de notre sujet, *dix minutes* après une injection *sous-cutanée d'adrénaline* (0,006 mg/kg), ne *présentait* pas d'inclinaison plus grande *qu'avant l'injection*, ni de trémolo (tremblement *de main*).

B. *Examen* de l'acuité auditive. Aucun symptôme d'hypoacousie ni du côté droit ni du *côté* gauche était remarqué.

C. Examens de l'équilibre et évolution des

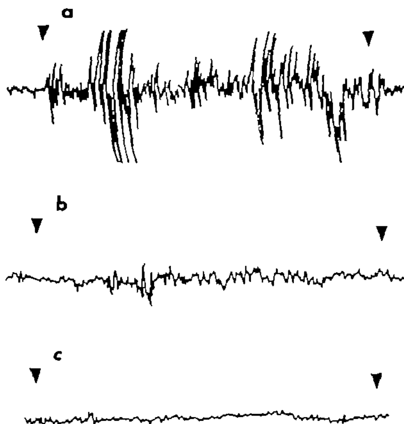


Fig. 1 Test de Mann ( ) Avant traitemen tendance à tomber en arrière avec les yeu ouverts et fermés. (*b*) 7 jours après quatrième procaïnisation une légè oscillation latérale a été observée les yeu ouverts au lieu de la tendance à tomber e arrière les yeux ouverts ou fermés. (*c*) 3 jours après la cinquième procaïnisation les troubles orthostatiques ont presqu disparu et cette amélioration dure encor après un mois.

sympyômes cérébrelleux ataxiques après fixation lombaire au moyen d un corset.

Note patiente, mise dans un corset, à éprouvé un soulagement des douleurs lombaires et un meilleur équilibre corporel.

Test de Mann la tendance qu avait montrée le sujet avant le traitement, à tomber en arrière les yeux ouverts avait disparu tandis que celle observée les yeux fermés est diminuée sans tout à fait disparaître

Test du nystagmus de position les mouvements horizontaux des yeux remarqués n ont présenté aucun changement après la fixation lombaire

Test du ynystagmus optocinétique et de poursuite d un objet en mouvement pas de changement.

Epreuve des index et épreuve du genou-talon le nombre d erreurs est diminué.

Epreuve des marionnettes aucune amélioration significative par l utilisation du croset, ni dans la pronation ni dans supination

Le résultat de ces examens montre bien que le fixation lombaire avec le corset apporte une certaine amélioration dans le fonctionnement de l équilibre et l etat ataxique du cervelet dont les symptômes sont observés aux membres supérieurs et inférieurs.

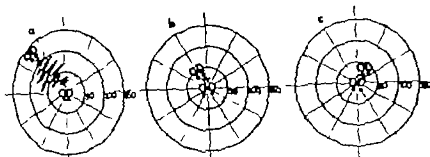
D Examens et évolution de l ataxie après la procaïnisation des muscles érecteurs lombaires.

Le résultat obtenu ici était meilleur que dans le cas d une fixation lombaire (ce qui signifie que le traitement par la procaïnisation lombaire est plus rationnel que la fixation lombaire).

Dans le cas qui nous préoccupe ici, le sujet a reçu cinq injections de 15 cc de solution à 1% de procaïne à raison d une fois par semaine

Avec chaque injection de procaïne la douleur lombaire était soulagée et la sensation de vertige diminuait. Parallèlement, les troubles orthostatiques, les mouvements anormaux des globes oculaires et la déviation des membres inférieurs se sont normalisés en même temps il ya eu une certaine amélioration dans l'ataxie des membres supérieurs.

Par exemple, dans le test de Mann, après la quatrième procaïnisation des muscles érecteurs lombaires, une légère oscillation latérale a été



... Test du piétinement de Fukuda. (a) Avant traitement : déviation en avant gauche, accompagnée d'ataxie. ... 7 jours après la quatrième procaïnisation : la distance de déviation comme l'angle de rotation vers la gauche ont diminué en même temps que les signes d'ataxie se sont réduits. ( ) 30 jours après la cinquième procaïnisation : le piétinement s'est normalisé sans jamais s'aggraver de nouveau pendant le mois qui suivait.

...servée les yeux ouverts au lieu de la tendance à tomber en arrière les yeux ouverts ou fermés, phénomène remarqué au début. Après la cinquième procaïnisation, les troubles orthostatiques avaient presque disparu et cette dernière amélioration dure encore après un mois. On voit Fig. 1 les enregistrement accélérométriques de chaque phase.

Dans le test du nystagmus spontané et de position, les petits mouvements horizontaux anormaux des globes oculaires qui étaient observés à la première visite ont disparu sans réapparaître après la troisième procaïnisation lombaire.

Quant à la déviation du piétinement accompagnée de signes d'ataxie notés avant le traitement, on a remarqué après la quatrième procaïnisation que la distance de déviation comme *l'angle de rotation vers la gauche ont diminué* en même temps que les signes d'ataxie se sont *réduits*. La cinquième procaïnisation terminée, le piétinement s'est normalisé sans jamais s'aggraver de nouveau pendant le mois qui suivait. On voit Fig. 2 le résultat schématisé du test du piétinement à chaque stade.

Pour les tests du nystagmus optocinétique et de poursuite d'un objet en mouvement, observation normale comme d'ailleurs avant le traitement.

Lors du premier examen, la pronation et la supination étaient maladroites aux membres supérieurs, surtout à gauche, si bien qu'elles étaient en état d'hypodiadochocinésie. Après la quatrième procaïnisation des muscles érecteurs lombaires elles se sont normalisées au membre supérieur droit, mais celles du membre supérieur gauche manquet encore d'habilité. Après la cinquième, elles sont devenues *tout à fait normales* à gauche comme à droite. Cette dernière amélioration se prolonge encore pendant un mois.

Dans l'épreuve des index, au lieu de 7 erreurs sur 10 essais enregistrées au début, on n'en a relevé 3 après la troisième procaïnisation et 2 après la cinquième.

L'épreuve de l'index-nez dont le résultat avait été normal avant le traitement ne changeait pas après la procaïnisation.

Dans l'épreuve du genou-talon, le nombre des erreurs qui était avant le traitement de 4 sur 10 essais pour la jambe droite et de 5 sur 10 pour la *gauche, diminuait au cours du traitement par* la procaïnisation à savoir après la cinquième procaïnisation la jambe droite n'a plus commis qu'une seule erreur ainsi que la jambe gauche.

La Fig. 3 montre deux courbes de fréquence de diminution du *réflexe H* aux membres inférieurs, l'une tracée en ▲ étant celle avant le traitement et l'autre tracée en ● étant celle après la cinquième procaïnisation. La courbe en ▲ montre qu'il y a suppression pour chaque fréquence aux stimuli électriques répétés, ce qui est *qualifié* par Ioku de troubles de type cérébelleux. Après la cinquième procaïnisation la suppression, notamment celle pour les fréquences basses comme on le voit, *s'est effacée et la* courbe est à peu près normale.

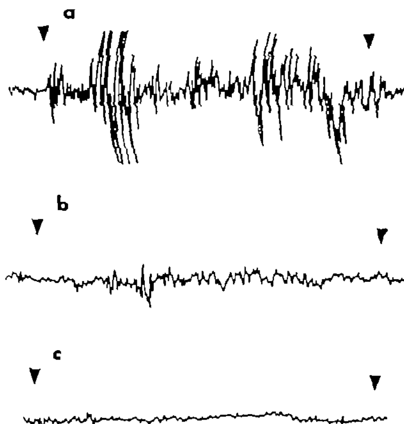


Fig. 1 Test de Mann (*a*) Avant traitement tendance à tomber en arrière avec les yeux ouverts et fermés. (*b*) 7 jours après la quatrième procaïnisation une légère oscillation latérale a été observée les yeux ouverts au lieu de la tendance à tomber en arrière les yeux ouverts ou fermés. (*c*) 30 jours après la cinquième procaïnisation les troubles orthostatiques ont presque disparu et cette amélioration dure encore après un mois.

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D Examens et évolution de l ataxie après la *procaïnisation des muscles érecteurs lombaires.*

Le résultat obtenu ici était meilleur que dans le cas d une fixation lombaire (ce qui signifie que le traitement par la procaïnisation lombaire est plus rationnel que la fixation lombaire).

Dans le cas qui nous préoccupe ici le sujet a reçu cinq injections de 15 cc de solution à 1% de procaïne, à raison d une fois par semaine.

Avec chaque injection de procaïne la douleur lombaire était soulagée et la sensation de vertige diminuait Parallèlement les troubles orthostatiques, les mouvements anormaux des globes oculaires et la déviation des membres inférieurs se sont normalisés en même temps il ya eu une certaine amélioration dans l ataxie des membres supérieurs.

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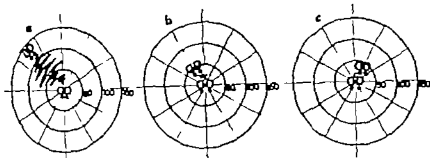


Fig. 2 Test du piétinement de Fukuda ( ) Avant traitement déviation en avant gauche, accompagnée d'ataxie. (*b*) 7 jours après la quatrième procaïnisation la distance de déviation comme l'angle de rotation vers la gauche ont diminué en même temps que les signes d'ataxie se sont réduits. (*c*) 30 jours après la cinquième procaïnisation le piétinement s est normalisé sans jamais s aggraver de nouveau pendant le mois qui suivait.

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Quant à la déviation du piétinement accompagnée de signes d'ataxie notés avant le traitement, on a remarqué après la quatrième procaïnisation que la distance de déviation comme l'angle de rotation vers la gauche ont diminué en même temps que les signes d'ataxie se sont réduits. La cinquième procaïnisation terminée, le piétinement s est normalisé sans jamais s aggraver de nouveau pendant le mois qui suivait. On voit Fig. 2 le résultat schématisé du test du piétinement à chaque stade

Pour les tests du nystagmus optocinétique et de poursuite d'un objet en mouvement observation normale comme d ailleurs avant le traitement.

Lors du premier examen, la pronation et la supination étaient maladroites aux membres supérieurs, surtout à gauche, si bien qu elles étaient en état d'hypodiadochocinésie. Après la quatrième procaïnisation des muscles érecteurs lombaires elles se sont normalisées au membre supérieur droit, mais celles du membre supérieur gauche manquent encore d'habilité. Après la cinquième, elles sont devenues tout à fait normales à gauche comme à droite. Cette dernière amélioration se prolonge encore pendant un mois.

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Dans l'épreuve du genou-talon le nombre des erreurs qui était avant le traitement de 4 sur 10 essais pour la jambe droite et de 5 sur 10 pour la gauche, diminuait au cours du traitement par la procaïnisation à savoir après la cinquième procaïnisation la jambe droite n a plus commis qu une seule erreur ainsi que la jambe gauche.

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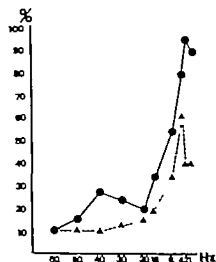


Fig 3 Courbes de fréquence de diminution du réflexe H aux membres inférieurs. ▲ Avant traitement ● après traitement.

Pour résumer ce qui précède, je crois pouvoir dire que la procaïnisation apporte une amélioration dans l étant vertigineux, laquelle est d ailleurs confirmée par les tests portant sur le fonctionnement de l équilibre aussi bien que par le fait que les signes ataxiques cérébelleux observés aux membres supérieurs et inférieurs ont diminué parallèlement à cette amélioration.

Voici maintenant deux cas dans lesquels le sujet était traité pendant assez longtemps par la procaïnisation et dont l observation de l évolution est plus complète que celle du premier cas. L anamnèse et le résultat du traitement de chaque cas sont décrits comme suit.

Cas 2 K.O., ♂ 53 ans, traumatisme cervical. Impliqué dans un accident de voiture, collision arrière, dans lequel le sujet n a pas reçu de choc à la tête et n a pas eu de troubles nerveux. Dès le troisième jour sont apparus la sensation vertigineuse, les douleurs nucales et la sensation de tête lourde Au bout de 8 jours il avait des douleurs dans la région lombaire dont l acuité allait augmentant avec la sensation vertigineuse. Malgré le traitement reçu dans une clinique, pas de soulagement, ce qui l a conduit dans notre service

L ensemble des résultats de la première visite et après fixation lombaire par un corset est consigné dans le tableau I

Après traitement par la fixation lombaire au moyen d un corset les douleurs lombaires et la sensation vertigineuse sont soulagées et le résultat des tests orthostatiques et du piétinement de Fukuda s est amélioré. D après les tests, épreuve des index, épreuve de l index-nez, épreuve des marionnettes, épreuve du genou-talon, on peut dire qu il existe une certaine amélioration dans l'ataxie.

Les résultats mentionnés précédemment nous ont conduit a essayer sur ce malade un traitement par procaïnisation lombaire qui nous paraissait valable. Nous avons donc procédé à neuf injections de 15 cc de solution à 1% de procaïne, à raison d une fois par semaine, de la région lombaire droite. On en voit le résultat dans le tabeau I. A quelques différences près chaque procaïnisation à apporté une amélioration tant dans le fonctionnement de l équilibre que dans l'ataxie cérébelleuse.

Bien que l efficacité de la procaïnisation ne soit pas aussi visible dans ce cas ci que dans le cas précédent, il est toujours constaté que chaque test a donné un meilleur résultat assez significatif pour pouvoir confirmer que le traitement par la procaïnisation est digne d être adopté.

Cas 3 K.M., ♀ 26 ans, traumatisme cervical. Accident de voiture, collision arrière, le patient garde la conscience claire bien qu il ait reçu un léger choc derrière la tête. Dès le lendemain sont apparues des sensations de contractures de la région cervicale et de tête lourde Au bout de 8 jours il commençait à se plaindre de douleurs lombaires en même temps que sont apparues sensations vertigineuses (titubations) céphalées, douleurs nucales.

Après la fixation lombaire par un corset le vertige et les douleurs lombaires ont diminué (Tableau II). Amélioration dans le résultat des tests d orthostatisme et du piétinement. La pronation et la supination des membres supérieurs n ont pas retrouvé leur habileté restant toujours en état d hypodiadochocinésie. Il y a eu une amélioration dans l épreuve des index et de l index nez mais pas de changement significatif dans l épreuve du genou-talon.

Tableau I

Test de Mann tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés, ± vacillement ou chute lorsque les yeux sont fermés, ± léger vacillement les yeux fermés qui n'aboutit pas à la chute; − normale

Nystagmus spontané et de position − normal

Epreuve des index, épreuve de l'index-nez, épreuve du genou-talon Sur 10 essais qui constituent le dénominateur le nombre d'erreurs représente le numérateur. Par conséquent 7/10 dans le tableau signifie qu'il y a eu 7 erreurs sur 10 essais. G, main gauche; D main droite; hypo, hypodiadochocinésie

Anamnèse et examen		Changement des fonctions d'équilibre et des symptômes cérébelleux à la suite du traitement par la procaïnisation des muscles érecteurs lombaires			
		Avant traitement		Après traitement	
		Sans corset	Avec corset	7 jours après 4ᵉ procaïnisation	7 jours après 5ᵉ procaïnisation
Lombago		+	±	+	±
Douleur sacrale		+	+	+	+
Réflexes d'orthostatisme (Test de Mann)		+ +	+	+	±
Nystagmus spontané et nystagmus de position			−	−	−
Test du piétinement de Fukuda					
Direction de la déviation		Droite	Gauche	Droite	Droite
Distance		50 cm	80 cm	20 cm	30 cm
Angle de rotation de l'axe du corps		30°	50°	20°	10°
Ataxie			±	+	±
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement	Légère amélioration
Epreuve des index		10/10	6/10	7/10	6/10
Epreuve de l'index-nez	D	10/10	6/10	7/10	7/10
	G	10/10	7/10	8/10	7/10
Epreuve des marionnettes	D	Hypo	Hypo	Hypo	Hypo
	G	Normal	Normal	Normal	Normal
Epreuve du genou-talon	D	2/10	1/10	2/10	1/10
	G	3/10	2/10	2/10	2/10

Les observations mentionnées antérieurement nous ont permis de penser que la procaïnisation de la partie douloureuse des lombes pouvait être un traitement valable du vertige et de l'ataxie dans ce cas. Nous avons donc procédé à cinq injections de 20 cc de solution à 1 de procaïne à raison d'une fois par semaine. On voit l'effet de ce traitement indiqué en comparaison avec les états antérieurs dans le tableau II. La sensation vertigineuse, les douleurs lombaires ont été soulagées par ce traitement. Bien qu'encore insuffisante une amélioration a été apportée dans les tests d'équilibre. Je crois aussi pouvoir dire que l'ataxie est elle aussi en voie de guérison après ce traitement. Il est particulièrement remarquable que le nombre des erreurs dans les épreuves des index ou de l'index-nez soit diminué de presque la moitié.

Des expériences de ces trois cas nous avons tiré les remarques suivantes

- les troubles du fonctionnement de l'équilibre et de l'ataxie cérébelleuse qu'on observe habituellement dans le cas de vertige traumatique accompagné de douleurs lombaires peuvent être traités efficacement par la procaïnisation de la partie douloureuse des lombes.
- on peut adopter ce traitement lorsque la *fixation* lombaire au moyen d'un corset apporte une amélioration dans le fonctionnement de l'équilibre et un soulagement dans l'ataxie cérébelleuse
- bien qu'il soit efficace ce traitement ne peut pas être déclaré la dernière thérapeutique possible du vertige traumatique pour lequel d'autres traitements seront à envisager

Tableau II

Test de Mann ++ Tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés + vacillement ou chute lorsque les yeux sont fermés ± léger vacillement les yeux fermés qui n aboutira pas à la chute − normale
Nystagmus spontané et de position − normal
Epreuve des index, épreuve de l index nez, épreuve du genou-talon Sur 10 essais qui constituent le dénominateur le nombre d'erreurs représente le numérateur Par conséquent 7/10 dans le tableau signifie qu'il y a eu 7 erreurs sur 10 essais. *G main gauche D main droite hypo, hypodiadochocinésie*

Anamnese et examens		Changement des fonctions d équilibre et des symptômes cérébelleux à la suite du traitement par la procaïnisation des muscles érecteurs lombaires		
		Avant traitement		Après traitement
		Sans corset	Avec corset	7 jours après 4ᵉ procaïnisation
Lumbago		+	±	±
Douleur nucale		+	+	±
Réflexes d'orthostatisme (Test de Mann)		++	+	+
Nystagmus spontané et nystagmus de position		−	−	−
Test du piétinement de Fukuda				
Direction de la déviation		Droite	Droite	Droite
Distance		120 cm	70 cm	110 cm
Angle de rotation de l'axe du corps		90	30°	80
Ataxie		+	±	±
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement
Epreuve des index		7/10	5/10	4/10
Epreuve de l'index nez	D	5/10	4/10	2/10
	G	3/10	1/10	1/10
Epreuve des marionnettes	D	Normal	Normal	2ormal
	G	Hypo	Hypo	Hypo
Epreuve du genou-talon	D	1/10	1/10	1/10
	G	1/10	1/10	1/10

Les considérations que nous avons faites sur ces trois premiers cas nous ont conduit a essayer d accompagner notre traitement d une autre thérapeutique Ainsi dans le quatrième cas que nous allons maintenant considérer le patient va être traité conjointement par la procaïnisation et par la traction des lombes. Car malgré son efficacité momentanée la procaïnisation n a apporté, dans notre dernier cas, qu un effet peu durable Le renouvellement de la procaïnisation, en outre nous a semblé avoir peu de chance de pouvoir prolonger l effet initial. Nous avons été pour ainsi dire obligé d adopter un autre traitement

Cas 4 I H., ♂ 24 ans, traumatisme cervical. La voiture du patient a été tamponnée par celle qui suivait. Au moment de l accident il n a pas eu conscience du coup qu il a reçu à la tête sans avoir perdu connaissance Dès le lendemain de l accident la nausée les douleurs nucales sont apparues. Au bout d environ un mois il a commencé à se plaindre de douleurs lombaires droites de vertige (sensation de vacillation corporelle), de mal de tête et de sensation de tête lourde Tous ces symptômes ont été améliorés par une thérapeutique vitaminée B1 B12 et A T P Néanmoins, la reprise des douleurs lombaires droites, cervicales, accompagnées de vertige et d une démarche ébrieuse l amène à notre clinique ou il est hospitalisé

La fixation des lombes avec un corset a apporté chez notre sujet un soulagement de son vertige, de sa sensation de titubation et une amélioration dans le résultat des tests de la fonction d équilibre et de l ataxie cérébelleuse (Tableau III)

Partant des résultats des observations précé-

Tableau III

Test de Mann: + +, tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés; +, vacillement ou chute lorsque les yeux sont fermés; ±, léger vacillement les yeux fermés *qui n'aboutira pas à la chute*; −, normale.
Nystagmus spontané et de position: −, normal.
Epreuve des index, épreuve de l'index-nez, épreuve du genou-talon: Sur 10 essais qui constituent le dénominateur le nombre d'erreurs représente le numérateur. Par conséquent 7/10 dans le tableau signifie qu'il y a eu 7 erreurs sur 10 essais. G, main gauche; D, main droite; hypo, hypodiadochocinésie.

Anamnèse et examens		Changement des fonctions d'équilibre et des symptômes cérébelleux à la suite du traitement par traction lombaire			
		Avant traitement			Après traitement
		Sans corset	Avec corset	20 minutes après la procaïnisation	Après 20 jours de traction lombaire
Lumbago		+	±	−	−
Douleur nucale		+	+	+	+
Réflexes d'orthostatisme (Test de Mann)			+	+	−
Nystagmus spontané et nystagmus de position		Mouvement anormal	Pas de changement	Pas de changement	−
Test de piétinement de Fukuda					
Direction de la déviation		Droite	Droite	Droite	Gauche
Distance		90 cm	50 cm	50 cm	40 cm
Angle de rotation de l'axe du corps		120°	90°	40°	0°
Ataxie			+	±	−
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement	Pas de changement
Epreuve des index		10/10	7/10	4/10	4/10
Epreuve de l'index-nez	D	3/10	2/10	0/10	0/10
	G	5/10	1/10	2/10	1/10
Epreuve des marionnettes	D	Hypo	Pas de changement	Amélioration	Amélioration
	G	Hypo			
Epreuve du genou-talon	D	3/10	4/10	1/10	1/10
	G	1/10	1/10	0/10	0/10

dentes nous avons pensé convenable de pratiquer un traitement par la procaïnisation de la partie douloureuse des lombes et nous avons procédé à l'injection de solution à 1 % sous un volume de 20 cc au total dans le lombe droit: 10 cc au niveau de L3, 10 cc au niveau de L4 (Tableau III, Fig. 4*a*, *b* et 5*a*, *b*.)

Comme dans les trois cas précédents la procaïnisation des muscles érecteurs lombaires a apporté dans ce quatrième cas une amélioration des tests examinant la fonction de l'équilibre et un soulagement de l'état ataxique cérébelleux. Mais l'effet de la procaïnisation dans ce cas était d'une durée tellement courte que le sujet retombait dans l'état antérieur deux jours après l'injection. Nous avons quand même essayé encore trois procaïnisations successives qui n'ont pas changé les résultats. Nous avons donc été obligé d'employer un autre traitement que celui par procaïnisation et nous avons choisi la traction des lombes. Le sujet était mis sur un lit incliné, recevant une traction de 6 kilos continuellement pendant les dix premiers jours, et huit heures par jour pendant les dix jours suivants. A la fin de ce traitement notre patient a témoigné d'un soulagement des douleurs lombaires et du vertige. A telle enseigne qu'à la longue il ne s'en plaignait presque plus. Voici le résultat des examens portant sur la fonction d'équilibre, il est identique à celui obtenu 20 minutes après la procaïnisation mais avec cette différence que cette fois l'effet du traitement dure plus longtemps. Les examens effectués après un recul de 20 jours sont consignés dans le tableau III et Fig. 4*a*, *c* et 5*a*, *c*. Nous pouvons dire que dans ce cas la traction des lombes a pu apporter un

Tableau II

Test de Mann + + Tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés, + vacillement ou chute lorsque les yeux sont fermés ± léger vacillement les yeux fermés qui n aboutira pas à la chute; − normale

Nystagmus spontané et de position − normal

Epreuve des index, épreuve de l'index-nez, épreuve du genou-talon Sur 10 essais qui constituent le dénominateur le nombre d erreurs représente le numérateur Par conséquent 7/10 dans le tableau signifie qu'il y a eu 7 erreurs sur 10 essais. G main gauche D main droite hypo, hypodiadochocinésie

Anamnese et examens		Changement des fonctions d équilibre et des symptômes cérébelleux à la suite du traitement par la *procaînisation des muscles érecteurs lombaires*		
		Avant traitement		Après traitement
		Sans corset	Avec corset	7 jours après 4 procaînisation
Lumbago		+	±	±
Douleur nucale		+	+	±
Réflexes d'orthostatisme (Test de Mann)		+ +	+	+
Nystagmus spontané et nystagmus de position		−	−	−
Test du piétinement de Fukuda				
Direction de la déviation		Droite	Droite	Droite
Distance		120 cm	70 cm	110 cm
Angle de rotation de l'axe du corps		90°	30°	80°
Ataxie		+	±	±
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement
Epreuve des index		7/10	5/10	4/10
Epreuve de l'index-nez	D	5/10	4/10	4/10
	G	3/10	1/10	1/10
Epreuve des marionnettes	D	Normal	Normal	Normal
	G	Hypo	Hypo	Hypo
Epreuve du genou-talon	D	1/10	1/10	1/10
	G	1/10	1/10	1/10

Les considérations que nous avons faites sur ces trois premiers cas nous ont conduit a essayer d accompagner notre traitement d une autre thérapeutique *Ainsi dans le quatrième cas que* nous allons maintenant considérer le patient va être traité conjointement par la procaînisation et par la traction des lombes. Car malgré son *efficacité momentanée*, la *procaînisation* n a apporté, dans notre dernier cas, qu un effet peu durable Le renouvellement de la procaînisation en outre, nous a semblé avoir peu de chance de pouvoir prolonger l effet initial Nous avons été pour ainsi dire obligé d adopter un autre traitement

Cas 4 I H ♂ 24 ans, traumatisme cervical La voiture du patient a été tamponnée par celle qui suivait. Au moment de l accident il n a pas eu conscience du coup qu il a reçu à la tête sans avoir perdu connaissance Dès le lendemain de l accident la nausée, les douleurs nucales sont apparues Au bout d environ un mois il a *commencé à se plaindre de douleurs lombaires* droites, de vertige (sensation de vacillation corporelle), de mal de tête et de sensation de tête lourde Tous ces symptômes ont été améliorés *par une thérapeutique vitaminée* B1 B12 et A T P Néanmoins, la reprise des douleurs lombaires droites cervicales, accompagnées de vertige et d une démarche ébrieuse l amène à notre clinique ou il est hospitalisé

La fixation des lombes avec un corset a apporté chez notre sujet un soulagement de son vertige de sa sensation de titubation et une amélioration dans le résultat des tests de la fonction d équilibre et de l ataxie cérébelleuse (Tableau III).

Partant des résultats des observations précé-

Tableau III

Test de Mann + tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés, + vacillement ou chute lorsque les yeux sont fermés, ± léger vacillement les yeux fermés qui n'aboutit pas à la chute; − normale

Nystagmus spontané et de position − normal

Epreuve des index, épreuve de l'index-nez, épreuve du genou-talon Sur 10 essais qui constituent le dénominateur le nombre d'erreurs représente le numérateur Par conséquent 7/10 dans le tableau signifie qu'il y a eu 7 erreurs sur 10 essais. G, main gauche; D, main droite; hypo, hypodiadochocinésie

Anamnèse et examens		Changement des fonctions d'équilibre et des symptômes cérébelleux à la suite du *traitement par traction lombaire*			
		Avant traitement			Après traitement
		Sans corset	Avec corset	20 minutes après la procaïnisation	Après 20 jours de traction lombaire
Lumbago			±	−	−
Douleur sacrale			+	+	
Réflexes d'orthostatisme (Test de Mann)			+	+	−
Nystagmus spontané et nystagmus de position		Mouvement anormal	Pas de changement	Pas de changement	
Test du piétinement de Fukuda					
Direction de la déviation		Droite	Droite	Droite	Gauche
Distance		90 cm	50 cm	50 cm	40 cm
Angle de rotation de l'axe du corps		120	90°	40	0°
Ataxie			−	±	−
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement	Pas de changement
Epreuve des index		10/10	7/10	4/10	4/10
Epreuve de l'index-nez	D	3/10	2/10	0/10	0 10
	G	5/10	1/10	2/10	1/10
Epreuve des marionnettes	D	Hypo	Pas de changement	Amélioration	Amélioration
	G	Hypo			
Epreuve du genou-talon	D	3 10	[illegible]10	1/10	1/10
	G	1 10	1 10	0/10	0 10

[illegible] nous avons pensé convenable de pratiquer un traitement par la procaïnisation de la partie douloureuse des lombes et nous avons procédé à l'injection de solution à 1 [illegible] sous un volume de 20 cc au total dans le lombe droit 10 cc au niveau de L3, 10 cc au niveau de L4 (Tableau III Fig 4*a*, *b* et 5*a*, *b*)

Comme dans les trois cas précédents la procaïnisation des muscles érecteurs *lombaires* a apporté dans ce quatrième cas une amélioration des tests examinant la fonction de l'équilibre et un soulagement de l'état ataxique cérébelleux. Mais l'effet de la procaïnisation dans ce cas était d'une durée tellement courte que le sujet retombait dans l'état antérieur deux jours après l'injection Nous avons quand même essayé encore trois procaïnisations successives qui n'ont pas changé les résultats. Nous avons donc été obligé d'employer un autre traitement que celui par procaïnisation et nous avons choisi la traction des lombes. Le sujet était mis sur un lit incliné, recevant une traction de 6 kilos continuellement pendant les dix premiers jours, et huit heures *par jour pendant les dix jours suivants. A* la fin de ce traitement notre patient a témoigné d'un soulagement des douleurs lombaires et du vertige. *A telle enseigne* qu'à la longue il ne s'en plaignait presque plus. Voici le résultat des examens portant sur la fonction d'équilibre Il est identique à celui obtenu 20 minutes après la procaïnisation mais avec cette différence que cette fois l'effet du traitement dure plus longtemps. Les examens effectués après un recul de 20 jours sont consignés dans le tableau *III* et Fig. 4*a*, *c* et 5*a*, *c*. Nous pouvons dire que dans ce cas la traction des lombes a pu apporter un

Tableau II

Test de Mann ++ Tendance à vaciller ou à tomber avec les yeux soit ouverts soit fermés + vacillement ou chute lorsque les yeux sont fermés ± léger vacillement les yeux fermés qui n aboutira pas à la chute, – normale
Nystagmus spontané et de position – normal
Epreuve des index, épreuve de l'index nez, épreuve du genou-talon Sur 10 essais qui constituent le dénominateur le nombre d erreurs représente le numérateur *Par conséquent 7/10 dans le tableau signifie qu il y a eu 7 erreurs sur 10 essais.* G main gauche D main droite hypo hypodiadochocinésie

Anamnese et examens		Changement des fonctions d équilibre et des symptômes cérébelleux à la suite du traitement par la procaïnisation des muscles érecteurs lombaires		
		Avant traitement		Après traitement
		Sans corset	Avec corset	7 Jours après 4ᵉ *procaïnisation*
Lumbago		+	±	±
Douleur nucale		+	+	±
Réflexes d'orthostatisme (Test de Mann)		++	+	+
Nystagmus spontané et nystagmus de position		–	–	–
Test du piétinement de Fukuda				
Direction de la *déviation*		*Droite*	*Droite*	*Droite*
Distance		1?0 cm	70 cm	110 cm
Angle de rotation de l'axe du corps		90°	30°	80°
Ataxie		+	±	±
Nystagmus optocinétique		Hypo-nystagmus	Pas de changement	Pas de changement
Epreuve des index		7/10	5/10	4/10
Epreuve de l'index-nez	D	5/10	4/10	?/10
	G	3/10	1/10	1/10
Epreuve des marionnettes	D	*Normal*	*Normal*	*?ormal*
	G	*Hypo*	*Hypo*	*Hypo*
Epreuve du genou-talon	D	1/10	1/10	1/10
	G	*1/10*	*1/10*	*1/10*

Les considérations que nous avons faites sur ces trois premiers cas nous ont conduit a essayer d accompagner notre traitement d une autre thérapeutique Ainsi dans le quatrième cas que nous allons maintenant considérer le patient va être traité conjointement par la procaïnisation et par la traction des lombes. Car *malgré son* efficacité momentanée, la procaïnisation n a *apporté, dans notre dernier cas, qu un effet peu* durable Le renouvellement de la procaïnisa tion en outre, nous a semblé avoir peu de chance de pouvoir prolonger *l effet initial* Nous avons été pour ainsi dire obligé d adopter un autre traitement.

Cas 4 I H., ♂ 24 ans, traumatisme cervical. La voiture du patient a été tamponnée par celle qui suivait. Au moment de l accident il n a pas eu *conscience du* coup qu il a reçu à la tête sans avoir perdu connaissance. Dès le lendemain de l accident la nausée les douleurs nucales sont apparues. Au bout d environ un mois il a commencé à se plaindre de douleurs lombaires droites, de vertige (sensation de vacillation corporelle) de mal de tête et de sensation de tête lourde Tous ces symptômes ont été améliorés par une thérapeutique vitaminée B1 B12 et A T P *Néanmoins,* la reprise des douleurs lombaires droites, cervicales, accompagnées de vertige et d une démarche ébrieuse l amène à *notre clinique où il est hospitalisé.*

La fixation des lombes avec un corset a apporté chez notre sujet un soulagement de son vertige de sa sensation de titubation et une *amélioration dans le résultat des tests de la fonction d équilibre et de l ataxie cérébelleuse* (Tableau III)

Partant des résultats des observations précé-

Tableau IV

Examens	Changement des fonctions d'équilibre et des symptômes cérébelleux à la suite du traitement par la procaïnisation des muscles érecteurs lombaires				
	Amélioration	*Pas changement*	Détérioration	Normal avant et après la procaïnisation	Note
Examens des fonctions d'équilibre					
Réflexe d'orthostatisme	21	7	0	0	
Test du piétinement de Fukuda	17	3	2	0	22 cas
Nystagmus optocinétique	4	10	0	4	18 cas
Examens des symptômes cérébelleux					
Epreuve des index	17	11	0	0	
Epreuve de l'index-nez	17	5	0	6	
Epreuve des marionnettes	14	8	0	6	
Epreuve du genou-talon	5	4	0	3	12 cas
Réflexe H	2	2	0	3	7 cas

dans le chapitre précédent, ainsi qu'à d'autres cas examinés, ce que je pense sur l'efficacité, comme traitement du vertigo traumatique accompagné d'ataxie cérébelleuse, de la procaïnisation des muscles érecteurs lombaires.

— La procaïnisation des muscles érecteurs lombaires est-elle efficace parmi les autres thérapeutiques possibles sur la région lombaire, comme traitement du vertige et de l'ataxie dans les cas de vertige traumatique accompagné de douleurs lombaires et de symptômes cérébelleux ?

Abstraction faite de différence de degré, les quatre cas exposés antérieurement montrent que l'injection de procaïne dans la région douloureuse lombaire peut apporter un soulagement ou une amélioration au vertige et à l'ataxie dont souffraient tous les sujets.

Nous avons essayé d'objectiver les suites de la procaïnisation pratiquée sur 28 cas, y compris les quatre cas déjà examinés, qui ont en commun cette particularité que tous les sujets se plaignent de douleurs unilatérales ou de prédominance unilatérale à la région lombaire en même temps que de vertige, en effectuant plusieurs test portant sur la fonction de l'équilibre et sur les symptômes cérébelleux ainsi qu'en interrogeant les sujets sur leur vertige. A l'issue de nos examens nous avons pu constater l'effet suivant la procaïnisation apporte dans la plupart des cas (21 sur 28 cas examinés) un soulagement au vertige, pour la plupart ils se plaignaient d'une certaine sensation de chancellement. Dans un certain nombre de cas il existe une restitution ad integrum. Il n'y a que 7 cas où elle n'a rien changé au vertige dont souffrait les sujets. Il est à remarquer toutefois qu'aucun cas n'a présenté d'aggravation de l'état vertigineux.

Les considérations statistiques sur l'évolution du résultat des examens de la fonction de l'équilibre observée à la suite de la procaïnisation sont consignées dans le tableau IV.

Nous croyons pouvoir dire que la procaïnisation de la partie douloureuse des lombes est un traitement efficace du vertige traumatique accompagné des douleurs lombaires et de symptômes cérébelleux. Il est en particulier remarquable de noter que le vertige ne se soit jamais aggravé à la suite de la procaïnisation. Il en est de même quant aux résultats des examens de la fonction d'équilibre et des symptômes cérébelleux. A ce propos il n'est pas superflu de rappeler le rapport de Hinoki et al. (1967) qui notait que la procaïnisation de la partie douloureuse du cou pouvait aggraver le vertige et l'ataxie. D'après mes propres expériences l'injection au niveau du cou à quelquefois apporté des aggravations. Il semble que la procaïnisation lombaire soit plus sûre que celle du cou, bien que le procédé soit identique dans les deux cas.

— *Le résultat obtenu dans les tests d'équilibre et d'ataxie cérébelleuse effectué après le traite-*

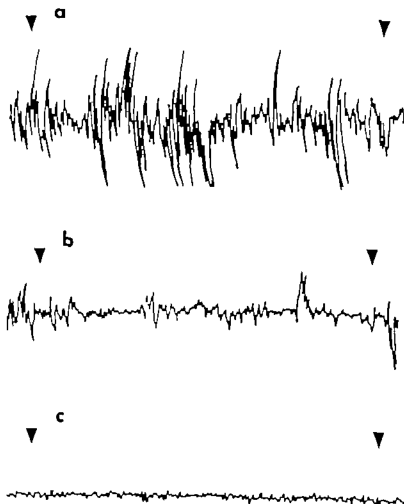


Fig 4 Test d orthostatisme (*a*) Avant traitement oscillations latérales et tendance à tomber soit les yeux ouverts soit les yeux fermés. (*b*) 20 minutes après la procaïnisation soulagement dans les douleurs des lombes et la sensation de vertige on voit une oscillation de la tête très diminuée. (*c*) Après 20 jours de tractions lombaires les mouvements violents de la tête ont pratiquement disparu.

soulagement des douleurs lombaires, du vertige, et une amélioration générale a quelques différences près selon les tests intérrogeant la fonction de l équilibre ou les symptômes ataxiques céré belleux observés aux membres supérieurs et inférieurs. Il faut remarquer comme nous l avons déjà dit que l effet de la traction était d une durée plus longue que celui de la procaïnisation

COMMENTAIRES

Je voudrais présenter ici, en me référant aux résultats obtenus dans les quatre cas considérés

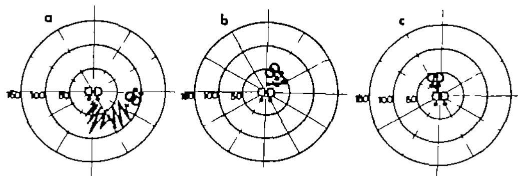


Fig 5 Test du piétinement de Fukuda (*a*) Avant traitement déviation en arrière droite accompagnée d ataxie. (*b*) 20 minutes après la procaïnisation la déviation vers l arrière du piétinement accompagnée d'ataxie s est amo ndrie visiblement par la procaïnisation, l'ataxie est diminuée et la direction du corps vers l'arrière se trouve maintenant vers l'avant. (*c*) Après 20 jours de tractions lombaires Il reste encore une légère déviation vers l'avant gauche mais le résultat obtenu ici est meilleur que celui obtenu 20 minutes après la procaïnisation, les symptômes d'ataxie observés pendant le piétinement ayant complètement disparu.

Tableau IV

Examens	Changement des fonctions d'équilibre et des symptômes cérébelleux à la suite du traitement par la procaïnisation des muscles érecteurs lombaires				
	Amélioration	Pas changement	Détérioration	Normal avant et après la procaïnisation	Note
Examens des fonctions d'équilibre					
Réflexe d'orthostatisme	21	7	0	0	
Test du piétinement de Fukuda	17	3	2	0	22 cas
Nystagmus optocinétique	4	10	0	4	*18 cas*
Examens des symptômes cérébelleux					
Epreuve des index	17	11	0	0	
Epreuve de l'index-nez	17	5	0	6	
Epreuve des marionnettes	14	8	0	6	
Epreuve du genou-talon	5	4	0	3	12 cas
Réflexe H	2		0	1	7 cas

dans le chapitre précédent, ainsi qu'à d'autres cas examinés, ce que je pense sur l'efficacité, comme traitement du vertige traumatique accompagné d'ataxie cérébelleuse, de la procaïnisation des muscles érecteurs lombaires.

— *La procaïnisation des muscles érecteurs lombaires est-elle efficace parmi les autres thérapeutiques possibles sur la région lombaire, comme traitement du vertige et de l'ataxie dans les cas de vertige traumatique accompagné de douleurs lombaires et de symptômes cérébelleux ?*

Abstraction faite de différence de degré, les quatre cas exposés antérieurement montrent que l'injection de procaïne dans la région douloureuse lombaire peut apporter un soulagement ou une amélioration au vertige et à l'ataxie dont souffraient tous les sujets.

Nous avons essayé d'objectiver les suites de la procaïnisation pratiquée sur 28 cas, y compris les quatre cas déjà examinés, qui ont en commun cette particularité que tous les sujets se plaignent de douleurs unilatérales ou de prédominance unilatérale à la région lombaire en même temps que de vertige, en effectuant plusieurs test portant sur la fonction de l'équilibre et sur les symptômes cérébelleux ainsi qu'en interrogeant les sujets sur leur vertige. A l'issue de nos examens nous avons pu constater l'effet suivant : la procaïnisation apporte dans la plupart des cas (21 sur 28 cas examinés) un soulagement au vertige, pour la plupart ils se plaignaient d'une certaine sensation de chancellement. Dans un certain nombre de cas il existe une restitution ad integrum. Il n'y a que 7 cas où elle n'a rien changé au vertige dont souffrait les sujets. Il est à remarquer toutefois qu'aucun cas n'a présenté d'aggration de l'état vertigineux.

Les considérations statistiques sur l'évolution du résultat des examens de la fonction de l'équilibre observée à la suite de la procaïnisation sont consignées dans le tableau IV.

Nous croyons pouvoir dire que la procaïnisation de la partie douloureuse des lombes est un traitement efficace du vertige traumatique accompagné des douleurs lombaires et de symptômes cérébelleux. Il est en particulier remarquable de noter que le vertige ne se soit jamais aggravé à la suite de la procaïnisation il en est de même quant aux résultats des examens de la fonction d'équilibre et des symptômes cérébelleux. A ce propos il n'est pas superflu de rappeler le rapport de Hinoki et al. (1967) qui notait que la procaïnisation de la partie douloureuse du cou pouvait aggraver le vertige et l'ataxie. D'après mes propres expériences l'injection au niveau du cou a quelquefois apporté des aggravations. Il semble que la *procaïnisation* lombaire soit plus sûre que celle du cou, bien que le procédé soit identique dans les deux cas.

— Le résultat obtenu dans les tests d'équilibre et d'ataxie cérébelleuse effectué après le traite-

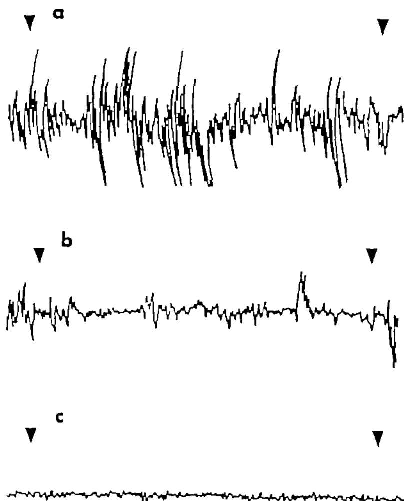


Fig 4 Test d orthostatisme (*a*) Avant traitement oscillations latérales et tendance à tomber soit les yeux ouverts soit les yeux fermés. (*b*) 20 minutes après la procaïnisation soulagement dans les douleurs des lombes et la sensation de vertige, on voit une oscillation de la tête très diminuée. (*c*) Après 20 jours de tractions lombaires les mouvements violents de la tête ont pratiquement disparu.

soulagement des douleurs lombaires, du vertige, et une amélioration générale a quelques différences près selon les tests intérrogeant la fonction de l équilibre ou les symptômes ataxiques céré belleux observés aux membres supérieurs et inférieurs. Il faut remarquer comme nous l avons déjà dit que l effet de la traction était d une durée plus longue que celui de la procaïnisation.

COMMENTAIRES

Je voudrais présenter ici en me référant aux résultats obtenus dans les quatre cas considérés

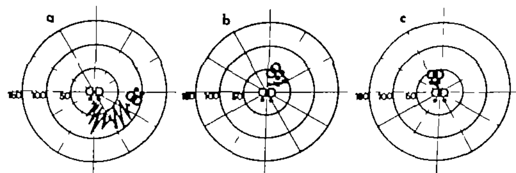


Fig 5 Test d piétinement de Fukuda (*a*) Avant traitement déviation en arrière droite accompagnée d ataxie. (*b*) 20 minutes après la procaïnisation la déviation vers l arrière du piétinement accompagnée d ataxie s est amoindrie visiblement par la procaïnisation, l'ataxie est dimi uée et la direction du corps vers l'arrière se trouve maintenant vers l'a ant. (*c*) Après 20 jours de tractions lombaires Il reste encore une légère déviation vers l'avant gauche mais le résultat obtenu ici est meilleur que celui obtenu 20 mi utes après la procaïnisation, les symptômes d ataxie observés pendant le piétinement ayant complètement disparu.

Tableau IV

Examens	Amélioration	Pas changement	*Détérioration*	Normal avant et après *la procaïnisation*	Note
	Changement des fonctions *d'équilibre et des symptômes cérébelleux* à la suite du traitement par la procaïnisation des muscles érecteurs lombaires				
Examen des fonctions d'équilibre					
Réflexe d'orthostatisme	21	7	0	0	
Test de piétinement de Fukuda	17	3	2	0	22 cas
Nystagmus optocinétique	4	*10*	*0*	4	18 cas
Examen des symptômes cérébelleux					
Epreuve des index	17	11	0	0	
Epreuve de l'index-nez	17	5	0	6	
Epreuve des marionnettes	14	8	*0*	6	
Epreuve du genou-talon	5	4	0	3	12 cas
Réflexe H	2	2	0	3	7 cas

dans le chapitre precédent, ainsi qu'à d'autres cas examinés, ce que je pense sur l'efficacité, comme traitement du vertige traumatique accompagné d'ataxie cérébelleuse, de la procaïnisation des muscles érecteurs lombaires.

— La procaïnisation des muscles érecteurs lombaires est-elle *efficace parmi* les autres thérapeutiques possibles sur la région lombaire, comme traitement du vertige et de l'ataxie dans les cas de vertige traumatique accompagné de douleurs lombaires et de symptômes cérébelleux ?

Abstraction faite de différence de degré, les quatre cas exposés *antérieurement* montrent que l'injection de procaïne dans la région douloureuse lombaire peut apporter un soulagement ou une amélioration au vertige et à l'ataxie dont souffraient tous les sujets.

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Les considérations statistiques sur l'évolution du résultat des examens de la fonction de l'équilibre observée à la suite de la procaïnisation sont consignées dans le tableau IV.

Nous *croyons pouvoir dire que* la procaïnisation de la partie douloureuse des lombes est un traitement efficace du vertige traumatique accompagné des douleurs lombaires et de symptômes cérébelleux. Il est en particulier remarquable de noter que le *vertige ne se soit* jamais aggravé à la suite de la procaïnisation il *en est de même* quant aux résultats des examens de la fonction d'équilibre et des symptômes cérébelleux. A ce propos il n'est pas superflu de rappeler le rapport de Hinoki et al. (1967) *qui* notait que la procaïnisation de la partie douloureuse du cou *pourrait aggraver le* vertige et l'ataxie. D'après mes propres expériences l'injec*tion au niveau* du cou à quelquefois apporté des aggravations. Il semble que la procaïnisation lombaire soit plus sûre que celle du cou, bien que le procédé soit identique dans les deux cas.

— Le résultat obtenu dans les tests d'équilibre et d'ataxie *cérébelleuse* effectué après le traite-

Tableau V *Corrélation entre le changement des réflexes d'orthostatisme par fixation lombaire (à l'aide d'un corset) et par la procaïnisation des muscles érecteurs lombaires*

Analyse de 19 cas de traumatismes cervicaux

	Procaïnisation		
Corset	Amélioration	Pas changement	Détérioration
Amélioration	13		0
Pas changement	4	0	0
Détérioration	0	0	0

ment par fixation des lombes au moyen d un corset peut il être un indice pour employer le traitement par procaïnisation ?

Dans un article publié antérieurement j'ai rapporté que la plupart des cas de vertige traumatique accompagné de douleurs des lombes pouvait être efficacement traité par le port d un corset qui pouvait apporter un soulagnement du vertige et une amélioration dans la fonction orthostatique (17 cas d amélioration sur 21) tandis que le corset ne pouvait rien changer dans le cas ou il n existait pas de douleurs lombaires (15 cas sans changement sur 22) (Ushio 1970) Ce fait a été confirmé par le résultat que nous avons exposé ci-dessus. On a observé une amélioration dans l état de vertige et de la fonction orthostatique due au port du corset dans 15 cas sur 19 lorsqu il existait des douleurs lombaires, il en est de même pour l évolution des symptômes cérébelleux (14 cas sur 19) Dans 5 cas il n y a pas eu de changement Les tableaux V et VI rendent compte de ces résultats. Pour savoir si le traitement par procaïnisation lombaire est ou non adaptable, le résultat satisfaisant obtenu par le port du corset dans les examens d équilibre et d ataxie cérébelleuse est un bon indice

— Comparaison des effets thérapeutiques, sur le vertige et le déséquilibre du corps y compris les symptômes cérébelleux, de la procaïnisation lombaire et cervicale

Lorsqu un individu est atteint d un traumatisme cervical il se produit des lésions fonctionnelles ou organiques des tissues de soutien mous cervicaux et lombaires provoquant une hypertonie de ces tissus. On a déjà rapporté, Hinoki (1970) Ushio (1970 1971), que cette hypertonie était une des plus importante cause de l'apparition du vertige et de l ataxie de l'équilibre qui accompagne le traumatisme cervical. Le mécanisme par lequel apparait le vertige dans les deux cas a peu près identiques est que le tissu mou de soutien cervical ou lombaire constitue un rapport détente — cable avec l hypothalamus et le tronc cérébral et que cette relation prend part dans l apparition des vertiges et de l ataxie. Les points de dissemblance proviennent de la fréquence de l apparition des symptômes cérébelleux qui est plus élevée dans le cas d'hypertonie du tissu de soutien mou cervical d une part, d autre part de la fréquence de guérison de l ataxie cérébelleuse qui est plus élevée par la fixation des lombes par un corset. On peut conclure que le propriocepteur cervical ou lombaire joue un rôle associé avec le cervelet dans l apparition du vertige du traumatisme cervical avec prédominance du propriocepteur lombaire Ce dernier cas va illustrer notre propos.

Cas 5 Y.A., ♂ 33 ans, traumatisme cervical La voiture du patient a été tamponnée. Il n a pas pris conscience du coup qu il reçu à la tête tout en gardant une conscience claire Dès le deuxième jour après l'accident sont apparus nausées, douleurs cervicales et un sentiment de tête lourde au bout d un mois successivement un lumbago droit et une sensation vertigineuse se

Tableau VI *Corrélation entre le changement des symptômes cérébelleux par fixation lombaire (à l'aide d'un corset) et par la procaïnisation des muscles érecteurs lombaires*

Analyse de 19 cas de traumatismes cervicaux

	Procaïnisation		
Corset	Amélioration	Pas changement	Détérioration
Amélioration	14	0	0
Pas changement	3	2	0
Détérioration	0	0	0

Tableau VII. *Effect du traitement du vertige et du déséquilibre par la procaïnisation lombaire et nucale*

N.P. Procaïnisation nucale, L.P. procaïnisation lombaire ↑ amélioration, ↔ pas de changement, ↓ détérioration
Normal, avant et après la procaïnisation, normale
Comparaison des 7 cas de traumatismes cervicaux

Cas	Age	Sexe	Vertige		Examens de symptômes cérébelleux		Test des réflexes d'orthostatisme		Test du piétinement de Fukuda		Nystagmus optocinétique	
			N.P	L.P	N.P	L.P	N.P	L.P	N.P	L.P	N.P	L.P
H.N.	39	♀	↑	↑	↔	↑	↑	↑	↑	↑	Normal	Normal
K.O.	53	♂	↑	↑	↔	↑	↔	↔	↑	↑	↑	↑
Y.A.	33	♂	↑	↑	↔	↑	↑	↑	↑	↑	↔	↔
M.K.	29	♂	↔	↑	↔	↑	↑	↑	↔	↑		↔
I.H.	24	♂	↑	↑	↔	↑	↔	↑	↑	↑		↔
H.S.	23	♀	↑	↑	↓	↔	↔	↑	↔	↔		↑
T.M.	21	♂	↔	←	↑	↑	↑	↑	↔	↑		
Résultats												
Amélioration			5	6	1	6	4	6	4	6		
Pas changements			2	1	5	1	3	1	3	1		
Détérioration			0	0	1	0	0	0	0	0		

font sentir. L'injection de procaïne dans la partie affectée du cou a eu pour effet de soulager les douleurs cervicales et d'améliorer le vertige et les troubles de l'équilibre. Par contre elle se montre peu efficace pour guérir l'ataxie cérébelleuse existante.

L'effet thérapeutique de la procaïne a perdu son efficacité en 24 heures. C'est pourquoi nous avons alors effectué la procaïnisation du lombe droit qui a amené la disparition des douleurs lombaires et un soulagement très visible dans la sensation de vertige.

Ce résultat nous permet de dire que la procaïnisation des lombes, à la différence de celle du cou, a un effet non seulement sur le résultat des examens portant sur la fonction de l'équilibre mais aussi sur l'amélioration de l'ataxie cérébelleuse. Ce résultat suggère que la procaïnisation cervicale dans ces cas bien qu'elle soit souvent utilisée, à une certaine limite.

Ces résultats ont été confirmés dans 7 autres cas identiques. Les patients se plaignaient de vertige, de douleurs cervicales et lombaires et présentaient des symptômes de la lignée cérébelleuse. Nous avons comparé les résultats obtenus après procaïnisation cervicale et lombaire avec un plus grand nombre de bons résultats après procaïnisation lombaire. Ce fait pourrait s'expliquer en partie parce que le propriocepteur lombaire est lié étroitement non seulement au tronc cérébral mais aussi au cervelet et que par conséquent les troubles orthostatiques et de la déviation du piétinement, tous les deux d'origine cérébelleuse, peuvent être supprimés par cette intervention. Cette hypothèse ne se contredit pas avec le fait que cette procaïnisation, par comparaison avec celle du cou, agit beaucoup plus efficacement sur les symptômes cérébelleux observés aux membres supérieurs et inférieurs. Pour ce qui est de l'effet exercé sur le nystagmus optocinétique par la procaïnisation cervicale et lombaire nous ne pouvons établir de comparaison en constatant que l'effet de la procaïnisation lombaire sera moindre sur le nystagmus que sur l'ataxie des membres supérieurs et inférieurs. Ce résultat permet de penser que les liaisons du propriocepteur lombaire d'une part avec le système des mouvements oculaires et d'autre part avec le réflexe spinal ne sont pas équivalentes mais qu'au contraire il est plus étroitement lié au système de réflexe spinal.

C'est sur l'ataxie cérébelleuse que la procaïnisation lombaire et cervicale diffère le plus. L'effet de la seconde donne sur l'ataxie cérébelleuse un résultat moindre que la première (Tableau VII).

Il faudra tenir compte de ces données lors du traitement du vertige et de l ataxie dans les cas de traumatismes cervicaux il ne suffira pas de traiter ce type de vertige uniquement par procaïnisation du cou mais il y aura intérêt à employer celle des lombes plus fréquemment

— Limites thérapeutiques de la procaïnisation des muscles érecteurs lombaires Conduite à tenir

D après le résultat obtenu il est évident que la procaïnisation de la partie affectée des lombes agit efficacement sur le vertige dû au traumatisme cervical. Il est aussi vraisemblable qu elle améliore le résultat des tests de la fonction d équilibre et en particulier ceux d orthostatisme ainsi que la déviation des membres inférieurs, elle diminue en outre les symptômes cérébelleux observés aux membres supérieurs et inférieurs. Dans la situation actuelle ou l on a pas encore de moyens puissants de guérir l ataxie cérébelleuse cette méthode sera digne d être employée plus fréquemment. La durée de l effet de la procaïnisation lombaire varie assez selon les cas Il y en a dans lesquels l effet d une seule injection dure plus de 8 jours et peut être prolongé plus longtemps par de nouvelles injections et d autres dans lesquels elle n a qu un effet assez court qui ne peut être prolongé par une nouvelle injection. Notre but à long terme sera de surmonter ce défaut A ce sujet nous avons fait deux ou trois expériences dont nous allons exposer ici l essentiel. La première consiste à mélanger lors de la procaïnisation des lombes, à la solution de procaïne de la Vitamine B ou du Stéroïd (Rindéron) Ce mélange à comme effet efficace de prolonger l effet de la procaïnisation, si bien que maintenant nous utilisons habituellement une solution à 1 % de procaïne mélangée à 2 mg de Stéroïd Mais ce précédé n est pas efficace dans les cas ou l'effet de la procaïnisation ne dure pas plus de quelques jours et ne peut être prolongé par des séries de procaïnisations. Ces derniers cas nous obligent alors à employer d autres procédés. Nous avons adopté le traitement par traction lombaires. A ce propos il faut rappeler que la traction cervicale doit être *évitée au début,* comme nous l avons souvent remarqué Ce conseil se fonde sur le fait que ce traitement pratiqué sur des sujets dont le traumatisme était récent provoquait très souvent une aggration du vertige et de l'ataxie. Il s appuie sur les résultats des examens expérimentaux sur l'animal montrant que le traumatisme cervical s accompagne au début de déchirures, d hémorragies et de dilatations du tissu mou de soutien cervical. Il en est autrement dans les cas ou le traumatisme est plus ancien, dans ces cas la traction du cou convenablement chargée peut exercer une bonne influence sur le vertige et l ataxie Hinoki (1969) *confirme ces résultats On peut aussi exercer une* traction des lombes dans ce cas je m impose les deux règles suivantes pour exercer cette traction

1 N'utiliser cette technique que dans le cas où le traumatisme est ancien ou dans les cas où le sujet se plaint de lumbago dans les jours qui suivent l accident.

2 N appliquer cette technique que dans les cas ou la procaïnisation de la partie douloureuse des lombes s est montrée éphémère et sans effet après d autres procaïnisations.

Je voudrais de toute façon m abstenir de présenter une conclusion définitive faute d expérience assez nombreuses pour le faire au sujet de la charge à donner et au moment d effectuer ce traitement Si le traitement pour l hypertonie du tissu de soutien mou cervical est applicable à l hypertonie du tissu mou de soutien lombaire, la stimulation de la partie douloureuse des lombes par ondes basses fréquences, la cathode étant placée à la partie douloureuse ou le badigeonnage de paraffine mérite d être essayés. Cette thérapeutique est une de nos préoccupations futures.

Nous avons constaté expérimentalement que le vertige traumatique s accompagne en même temps d une anomalie fonctionnelle du tronc cérébral et du cervelet (Ushio 1970 1971 1973). En vue de guérir l anomalie fonctionnelle du tronc cérébral la Centrophénoxine (Lucidril) et la CDP choline (Nicholin) ont été utilisées Les résultats de leur efficacité ont été consignés dans les travaux d Hinoki et al. (1967) et Ushio et *al (1970) Pour les cas accompagnés de troubles* du tronc cérébral il sera raisonnable d utiliser

ce médicament même si l'on est en présence de symptômes cérébelleux. Mais étant donné l'insuffisance d'efficacité au cours de nos propres expériences, du *traitement par l'utilisation exclusive* de ces médicaments, il est préférable d'utiliser en même temps un autre procédé intéressant les lombes par exemple la procaïnisation. L'utilisation associée médicament + procaïnisation donne un meilleur *résultat* que la procaïnisation seule. Il est nécessaire néanmoins d'avoir une plus grande expérience à ce sujet.

RÉSUMÉ

I. Nous avons pris pour sujets à examiner ceux souffrant de vertige traumatique accompagné de douleur lombaire (lumbago etc.) en même temps que de symptômes cérébelleux frustes. Nous avons procédé à un traitement par injection de procaïne dans la région douloureuse lombaire. Nous avons obtenu les résultats suivants

— il y a un grand nombre de patients qui ont témoigné à la suite de la procaïnisation de la partie douloureuse lombaire de la disparition du lumbago et d'un soulagement, voire même de la disparition du « vertige »

— pour un grand nombre de cas le résultat des examens portant sur le fonctionnement de l'équilibre (surtout du test d'orthostatisme et celui de déviation des membres inférieurs : test du piétinement) s'améliore en même temps que les symptômes cérébelleux frustes observés aux membres supérieurs et inférieurs s'amoindrissent.

— il faut tout de même distinguer deux cas dans l'un, l'injection a un effet relativement prolongé qui peut être encore poursuivi par la répétition de la procaïnisation, dans l'autre on observe le contraire la procaïnisation n'ayant qu'une courte vie et ne pouvant être renforcée par une autre injection. Dans ce dernier cas nous avons essayé comme traitement supplémentaire la traction lombaire par laquelle le vertige a été efficacement supprimé

— lors de la fixation des lombes par un corset, le fonctionnement orthostatique se trouve amélioré et les symptômes cérébelleux frustes diminués (vérification par les épreuves des index, de l'index-nez et des mouvements), alors la procaïnisation des lombes est à adopter comme traitement du vertige traumatique

II. Dans le cas où nous avons pris comme sujets à traiter ceux qui souffraient de vertige traumatique avec des douleurs cervicales et lombaires nous avons effectué les procaïnisations des parties affectées du cou et des lombes. Les résultats suivants ont été obtenus

— les procaïnisations du cou et des lombes ont servi toutes les deux à améliorer l'état de vertige en même temps que les résultats du test d'orthostatisme et de déviations des membres inférieurs (test du piétinement) dans bien des cas.

— en ce qui concerne les symptômes cérébelleux frustes la procaïnisation du cou était peu efficace, par contre celle des lombes s'est trouvée être efficace pour leur amélioration.

Les résultats obtenus semblent appuyer l'hypothèse que nous avons posée et que nous avons défendue dans nos publications suivant laquelle l'hypertonie du propriocepteur lombaire, tout en agissant sur l'anomalie fonctionnelle non seulement du tronc cérébral mais aussi du cervelet, participe à la genèse de l'ataxie de l'équilibre.

Les mêmes résultats semblent indiquer que la procaïnisation des muscles érecteurs lombaires mérite d'être employée pour supprimer le « vertige » dans les cas qui nous concernent.

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Acta Otolaryngol Suppl 330 144–146 1975

TUBING AS A TREATMENT FOR RECURRENT INFANT SUPPURATIVE OTITIS MEDIA

Yoshiki Hattori

Gifu, Japan

Abstract (1) The details described below have evidenced that the tubing therapy is an influential treatment for the recurrent infant suppurative otitis media. The tube with a beveled head and split shank is very convenient and effective for the treatment since it is not only easily inserted but also easily removed, preventing it from migration into the tympanum. (2) The treatment must promote the drainage of discharges through the infant auditory tubes which are thick and short and improve the ventilation of the middle ear cavity half permanently. (3) According to the author's experience, the spontaneous extrusion of the ideally set tube after 2 or 3 months is a sign of a perfect cure of this disease.

Since tympanostomy with a plastic tube was introduced in 1959 by Armstrong, many papers on this subject have been published and it has been generally recognized as an important otologic treatment. Nowadays, however the treatment is mainly applied to nonsuppurative middle ear diseases. The author has obtained good results by applying it to suppurative middle ear diseases of infants, namely to recurrent infant suppurative otitis media.

In many cases of infant suppurative otitis media, a drainage made by a myringotomy is generally closed after 2 or 3 days and the retention of purulent discharge occurs again in the middle ear cavity. On the other hand there are many cases of infant suppurative otitis media whose tympanic membrane seems to be cured by using antibiotics, but the disease recurs spontaneously by a slight upper airway infection. However if any perforation even a very small one like a pin hole remains after the pus has disappeared a recurrence of the inflammation rarely occurs, or even if a recurrence does occur it is mostly slight and can be cured in a short period. From a clinical viewpoint of such a schematic process of suppurative otitis media of infants the author presumed that the promotion of continuous ventilation of the middle ear cavity through a tympanostomy tube could prevent a recurrence of suppurative otitis media of infants.

SHAPE OF THE TUBE

Armstrong, Per Lee, Silverstein and others described an indication of the myringotomy with a plastic tube mainly for chronic nonsuppurative middle ear diseases. Therefore various shapes of the tube have been developed in order to be able to fix a tube, long and tight, through the tympanic membrane between the external meatus and tympanic cavity. However in cases of infant recurrent suppurative otitis media, the tube must be not only easily inserted but also easily removed because it drops out often spontaneously according to the cure of the disease. According to the author's experience 3 months are sufficient to keep the tube on the drumhead in order to obtain a perfect cure. Thus, a new type of tube was designed in 1971 by the author.

Fig. 1 illustrates the new polyethylene tube 10 mm long and 1 mm in diameter with a beveled head like a tympanum puncture needle. The tube can be inserted in a needle hole after a puncture or through a pin hole perforation which is ready to close. The split shank protects the tube from dropping into the tympanum and from obstruction by blood clot or secretion.



Fig. 1 Polyethylene tube which is used by the author (30 mm long and 1 mm in diameter).

APPLICATION OF THE TUBE

1 *Appropriate stage for tubing*

First of all, customary treatments for the suppurative otitis media must be performed. Aural discharge usually disappears in a week. At this stage, if any perforation remains, a tube should be inserted through the perforation. If the perforation is greater than the diameter of the tube, the insertion should be postponed untill the perforation decreases in size somewhat smaller than the tube diameter. Even in cases with a perforation which has been closed, a tympanum puncture often reveals a small amount of mucous secretion, so that a tube should be inserted through the needle hole made by the puncture on the drumhead.

2. *Anesthesia*

Local anesthesia is sufficient in most cases, namely an existing perforation of a drumhead or a needle hole by a puncture supplies a sufficient anesthesia through an ear bath with 4–8% Lidocain solution.

3. *Site of the tube application*

The anterior inferior quadrant is generally chosen as the site of application of the tube.

4. *Complication*

Complications that had been reported such as bleeding, obstruction of the tube were encountered but no new complications were observed.

5. *Microscope*

An operating microscope is necessary to perform a tube application efficiently.

CASES

The tubing was performed in 36 ears of 24 cases among 126 cases of infant suppurative otitis media, admitted from January 1971 to December 1973. They were infants from 6 months to 2 years of age averaging 1 year and 1 month.

Each one of the 24 cases had a previous history of recurrent suppurative otitis media treated with several myringotomies, tympanum punctures and antibiotics.

In 10 ears of 7 cases, mastoid antrums were still not clear radiographically although improvements were revealed in tympanic membranes. In 4 ears of 2 cases, multiple resistance was present in the sensitivity test of antibiotics. Two cases had significant allergic disposition. Two cases were affected measles during otitis media. Two cleft palate cases were included. The following 24 cases received the tubing therapy i.e. infant suppurative otitis media which recurred often in spite of the customary treatments such as intensive use of antibiotics, myringotomy tympanum puncture, use of steroid or enzyme and γ-globulin injections.

RESULTS

1. After the tube was set, 21 cases were affected with upper respiratory infection.

2. 22 ears of these 21 cases progressed satisfactorily without any aural discharge in spite of the upper respiratory infection which was cured after a few days. Then the tube was *extruded* spontaneously 2 or 3 months after the insertion and the drumhead showed a complete cure of the

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RESPONSES OF CORTICAL VESTIBULAR CENTER PRODUCED BY STIMULATION OF VESTIBULAR NUCLEI AND VISUAL ASSOCIATION AREA IN THE CAT

Satoru Watanabe, Hiroyasu Jijiwa and Kazuo Itoh[1]

Institute of Equilibrium Research, Gifu University School of Medicine, Gifu, Japan

Abstract. (1) The cortical projection of the vestibular nuclei (LVN, MVN and IVN) was investigated by the evoked potential and unit discharge analyses in the cat anesthetized with alpha-chloralose and/or immobilized with gallamine triethiodide. (2) This projection field coincided well with that of the vestibular nerves, being principally contralateral by LVN stimulation but nearly symmetrical by either MVN or IVN stimulation. (3) Of 11 units responsive to vestibular nuclei stimulation, 6 reacted to stimulation of the visual association cortex (anterior part of the Clare-Bishop area). The response pattern of the cortical vestibular units by C-B stimulation was a sequence of excitation, inhibition and rebound. (4) Interaction of visual information with the cortical vestibular neurons was discussed.

Many studies have been published on the primary cortical vestibular projection area which rely on evoked potential methods or single unit analysis involving stimulation of the vestibular nerve in the monkey (Fredrickson et al., 1966 Schwarz & Fredrickson, 1971*b* Schwarz et al., 1973), the cat (Walzl & Mountcastle 1949· Kempinsky 1951 Anderssen & Gernandt, 1954 Mickle & Ades, 1954 Milojevic & St. Laurent, 1966 Landgren et al 1967 Sans et al 1970), the rabbit (Ödkvist et al 1973) and the guinea pig (Ödkvist et al., 1973). In some of these animals it has been found that the area is adjacent to actually within the face region of the somatosensory cortex. Moreover in the monkey and the cat, the vestibular cortex, unlike other primary sensory areas, receives a convergence both from the vestibular and the somatosensory projection. The monkey vestibular field has been found to respond to both vestibular and kinesthetic (joint movement) stimuli or deep muscle pressure (Schwarz & Fredrickson 1971*a*) It has also been reported that the vestibular and somatosensory convergence exists even in the primary relay station of the vestibular nerve, in the vestibular nuclei (Fredrickson et al., 1966*b*). The convergence in the vestibular nuclei has been confirmed on the basis of postural and oculomotor reflex findings. On the other hand, the bimodal characteristics of the cortical vestibular field, as suggested by Fredrickson et al. (1966*a*), may signify that the motor regulation and conscious spatial orientation have a highly developed hierarchy of functional differentiation. In the present experiments, one goal was to ascertain whether the area responding to stimulation of the vestibular nuclei and having the bimodal characteristics, corresponds with the vestibular field which has been hitherto investigated by stimulation of the vestibular nerve.

The vestibular field reportedly extends over the anterior supra- and the anterior ectosylvian gyri, or on a circumference around the descending limb of the anterior suprasylvian sulcus. This region is just adjacent to the visual association area, V_m (Sanides & Hoffman, 1968), also named the Clare–Bishop area (Clare & Bishop, 1954). Concerning interaction between vestibular and visual information, vestibular influences upon visual sensation were already reported by some investigators (Grüsser et al., 1960· Kornhuber & Fonseca, 1964 Horn & Hill, 1969 Grüsser & Grüsser-Cornehls, 1972, Denney &

[1] Present address. Department of Anatomy Gifu University School of Medicine, Gifu, Japan.

inflammation without any perforation or with only a small pinhole perforation

3 In 3 ears, the early extrusion of the tube occurred within a month One ear showed a recurrence of aural discharge although the perforation had already been closed once. In the other 2 ears, the perforation remained but the disease was cured (A tube inserted incompletely was often extruded within a few days. Such cases are omitted from this paper)

4 In 2 ears which had neither involvement of acute upper respiratory infection nor recurrence of aural discharge the tube was not extruded spontaneously even after 3 months. The tube was removed by the author

5 The tube was swept out by and carried away to the external meatus by the massive aural discharge in 9 ears.

DISCUSSION

The reason for the effectiveness of the tubing is summarized from these results in the following three points.

1 *Ventilation*

It can be said that the 22 ears did not show any recurrence of a suppurative inflammation despite the acute upper respiratory infection because of the continuous ventilation of the middle ear cavity through the tube It can also be said that the spontaneous extrusion of the ideally set tube after 2–3 months accompanied with healing of the otitis media is the best result of this treatment.

2. *Drainage*

There is no evidence of a healing acquired by drainage of pus through the tube in these 24 cases Therefore by the tubing discharges contained in the middle ear cavity must be swept out and drainaged through the infant thick and short auditory tube. Just as the liquid in a pipet drops out by removing a finger which covers the upper end of the pipet, i.e. the drainage should be done through the auditory tube by the insertion of the tube, but not through the inserted tube.

3 *Fuse effect*

If a suppurative inflammation occurs in the ear in which the tube is inserted, the tube is washed out to the external meatus by the massive purulent discharge thus the drainage of purulent discharge is accomplished and it has same effect of an early stage myringotomy Per Lee described that "Six infectious episodes were unresponsive to topical and systemic antibiotic therapy and terminated only after the tube was removed Inflammatory hyperplasia granulation, and obstruction to drainage were the pathologic features in these cases. In other words, the effect of an inserted tube is easy dropping out by an acute suppurative inflammation and it corresponds to the effect of a fuse in an electric circuit It can be said that the tube turns off or reduces an exacerbation of disease and helps a spontaneous healing of an infant who is disposed to recurrent suppurative otitis media

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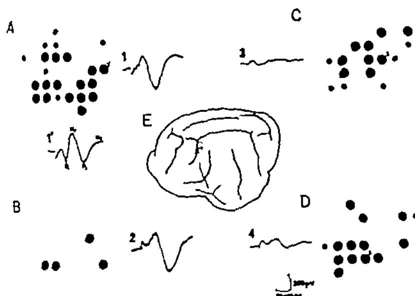


Fig. 1. Distribution of cortical responses to electrical stimulation of vestibular nuclei. A, C and D: distributions of responses to stimulation of contralateral LVN, MVN and IVN, respectively. B: ipsilateral LVN stimulation. Different-sized diameters of filled circles which respectively indicate (from larger to smaller) amplitude of each response is higher than 60 %, between 60–40 %, or lower than 40 % of maximal response for each *stimulation*. Unresponsive portions are indicated by open circles. Recording sites are shown by black dots in E. 1–4: typical evoked responses to each stimulation, the recorded sites of which *are indicated by the same numbers* in A–D. 1′: response evoked on AI area to contralateral LVN *stimulation*. See text for details. Upward deflection indicates negativity in this and all following figures.

At the termination of each experiment, the animals were anesthetized with Nembutal and perfused with 10 % formalin solution from the carotid artery and the whole brain was removed for histological study. Frozen and/or celloidin sections of the brain were cut at every 30 μ, and stained by Nissl technique.

RESULTS

1. *Projection Fields of Vestibular Nuclei*

(a) *Lateral vestibular nucleus*

The cortical projection field evoked by stimulation of contralateral LVN (Fig. 1A) was found to lie around the descending limb of the anterior suprasylvian sulcus (SSS). The main responding area was in the anterior suprasylvian gyrus. A typical evoked potential consisted of an initial positive and negative sequence followed by a large, slow positive deflection; two or three ripple-like wavelets sometimes appeared in an asceding slope of the initial positive–negative deflection. The earliest peak latency of negativity measured was 9.0 msec at a part just rostral to the SSS. The maximal amplitude was obtained in this part, reaching as high as 80 μV in negative deflection and 160 μV in slow positive one. In the region caudal to the SSS, which overlapped the region of auditory I (A I) as described by Thompson et al. (1963), there was a characteristic response composed of a sequence of potentials consisting of small negative (N_1), a large positive (P_1), a large negative (N_2), a large positive (P_2) and a large slow negative (N_3) component. The respective peak latency of each component was 5.6 msec, 10 msec, 13.3 msec, 21.1 msec and 33.2 msec. Distribution of this type of potential with the initial negative (N_1) and positive (P_1) sequence followed by the typical triphasic response did not extend to the rostral region beyond the SSS anteriorly. Since the stria acustica runs along the LVN, it might be simultaneously stimulated by the LVN

Adorjani, 1972). However investigation of the visual influences affecting vestibular sensation has been rarely reported except for one paper by Kornhuber (1972) But we do have some real life experience on the subject for example the fact that when a skilled ballet dancer in the course of a pirouette fixes his gaze upon some stationary object neither postrotatory nystagmus nor vertigo occurs (Fukuda & Tokita 1971). This is one noteworthy fact that encouraged the authors to investigate the underlying neural connection between the vestibular field and the visual association area Accordingly another goal of the present experiments was to make clear a direct connection and the interaction between the vestibular field and the visual association area.

MATERIALS AND METHODS

Experiments were performed on 14 cats weighing 2.4 kg to 4 0 kg. Eight were employed for estimation of the vestibular field six for unit analysis, and all were initially anesthetized with ketamine hydrochloride (Ketalar Parke Davis & Sankyo) 15–20 mg/kg administered intramuscularly Cannulae were inserted into the trachea for artificial respiration and the radial cutaneous vein for administration of drugs. The animals were placed in a stereotaxic frame and craniotomized to expose a part of the frontal cortex, the entire anterior suprasylvian and anterior ectosylvian gyri and a part of the visual cortex in the left hemisphere The cerebrospinal fluid was drained through a cisterna magna incision in order to reduce the movements of the brain To prevent drying, the exposed cortices were covered with 4 percent agar Ringer solution, except for a recording portion filled with liquid paraffin Body temperature was maintained by a heating pad Concentric needle electrodes with an outer electrode diameter of 1 0 mm and inner one of 0.5 mm and an interelectrode distance of 0 8 mm were used for stimulation These stimulating electrodes were inserted in the vestibular nuclei with the stereotaxic coordination modeled on the atlas of the cat brainstem (Berman, 1968) the lateral vestibular nucleus (LVN) P 7 L 4 depth −4 the medial vestibular nucleus (MVN) P 9 L 2.5 depth −3 the inferior vestibular nucleus (IVN) P 12, L 2.5 depth −4 Other stimulating electrodes were placed with naked eye on the visual association cortex, V_{ass} which lies on the medial bank of the middle suprasylvian sulcus (Clare–Bishop area, C-B), and on a macular region (middle portion of the area 17–18 border) and/or an upper part of the vertical meridian (anterior portion of the area 17 18 border) of the visual cortex. A stimulating square pulse of 0 01–0 05 msec duration at a frequency of 0 5–1 Hz was used and its intensity was varied from 1 to 30 V Before recording, the animals were re-anesthetized with alpha-chloralose (60 mg/kg) and/or immobilized with gallamine triethiodide (3 mg/kg/hr) Respiration was maintained artificially

Cortical evoked potentials were recorded monopolarly with a silver ball electrode from the pial surface of the anterior supra and ectosylvian gyri reference being made to the cranial skin detached from the skull. With the aid of a micromanipulator the electrode was moved with rectangular coordinates calibrated in millimeter units. The resulting evoked potentials of 40 successive stimuli were averaged by an ATAC 501 computer and photographed. In several experiments the depth potential profiles and unitary discharges were recorded with micropipettes filled with 1 5 M potassium citrate (resistance 3–10 meg ohms). The depth potentials were also averaged by computer while unitary discharges were stored on magnetic tapes, displayed on an oscilloscope and eventually filmed.

Electrolytic lesions were made at all stimulating sites. In order to confirm microelectrode tracks for the depth potential recording and unitary discharge analysis, the micropipette removed after recording was coated with china ink and reinserted into the cortex parallel together with but 1 mm apart from the recording track, so that direction of the electrode tracks could be proved histologically The depth from the cortical surface was read from a micrometer gauge on the micromanipulator

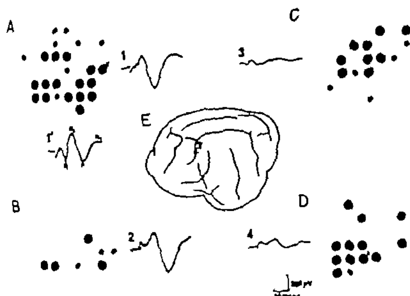


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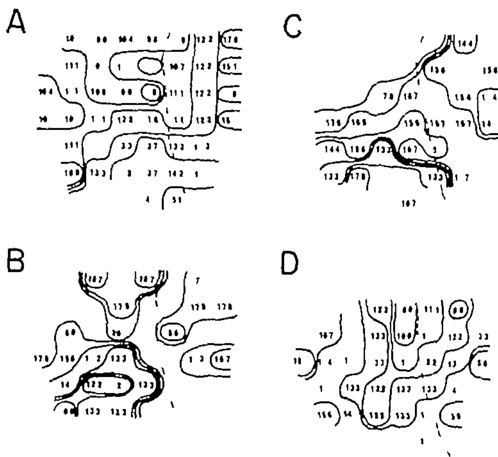


Fig 2 Contour map of latencies of evoked responses. A D same as in Fig. 1 Contour lines are drawn on the basis of the peak latencies of negative waves evaluated in msec. Dotted line indicates the suprasylvian sulcus.

electrode so this could possibly be an auditory response The second negativity (N_2) had a similar peak latency as the negativity of the triphasic typical potentials, seemingly derived from an analogous origin The contour map displaying topographical distribution of the peak latency of negativity (Fig. 2A) indicates that the region with shorter latency corresponds with the higher amplitude region rostral to the SSS In the region more lateral to A I the evoked re sponses took on the typical sequence of poten tials, although they showed abruptly decreasing amplitudes.

With ipsilateral LVN stimulation the active region was found somewhat more lateral to the parts responding to contralateral LVN stimula tion (Fig. 1B and Fig. 3A) The response was almost the same as for the contralateral one being formed by a triphasic sequence and having peak latencies of 11 1 msec for the negative and 20 0 msec for positive components in the shortest case The maximal amplitude was 30 μV and 160 μV respectively Topographical distribution of the peak latency and also of the amplitude of the negativity showed a slight difference between the ipsi- and contralateral responses, that is, the contralateral response was of shorter latency and of larger amplitude than the ipsilateral one. With the ipsilateral stimulation, the response with the largest amplitude and the shortest latency was elicited in more lateral region than with the contralateral one. This difference may be due to asymmetry of stimulating positions, but it is rather questionable whether a little difference in electrode positions could alter practically the active area even with stimulation of such high intensity as 20 V and duration of 0 03 msec. The evidence would imply that the variation originates from a characteristic of laterality

(b) Medial vestibular nucleus

The area activated by the MVN stimulation was found more lateral than by the LVN stimulation and located mainly rostral to the SSS (Fig. 1C and Fig. 3C). A typical potential consisted of triphasic small negative–positive and slow negative deflections (Fig. 1C–3). The maximal amplitude and the shortest latency of negativity measured was 60 μV and 13.3 msec, respectively.

(c) Inferior vestibular nucleus

The response evoked by IVN stimulation was characterized by two peaks of small negative and slow positive waves (Fig. 1D–4). The initial negative peak was 40 μV in amplitude and had a latency of 5.6 msec, and the second negative-positive sequence was 120 μV in amplitude. Topographical distributions of the magnitude of the second negative–positive sequence were shown in Figs. 1D (ipsilateral stimulation) and 3D (contralateral stimulation). The extent of the active region delineated by stimulation of IVN was more limited than that delineated by the LVN stimulation, but was almost as large as that by the MVN stimulation. The location of the active region by IVN stimulation was more lateral than by the MVN stimulation.

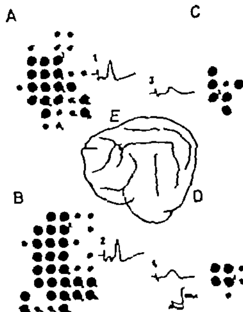


Fig. 3. Distribution of cortical responses to electrical stimulation of vestibular nuclei. A, C, D and B, distributions of responses to stimulation of ipsilateral LVN, MVN, IVN and contralateral LVN, respectively. Other was the same as in Fig. 1 except that the filled triangles indicate positive wave preceding the negative one, the larger triangles showing higher amplitude.

2. Cortical Depth Distribution of Potentials

The depth potential profiles illustrated in Fig. 4 are obtained by microelectrode inserted obliquely from the cortical surface to the lower bank of suprasylvian fold. The surface potential evoked by stimulation of contralateral LVN was distinguished by a negative wave with peak latency of 10 msec. As the electrode was advanced deeper from the surface, the negative wave diminished gradually up to a depth of 1 600 μ, while the preceding positive wave increased its amplitude and reached a maximum at depth of 000 μ. The phase reversal occurred at depths between 1 600 and 2 000 μ. At 3 000 μ, spike discharges appeared superimposed on the negative wave, and no further positive wave could be seen. At 4 000 μ, the spike activity was no longer seen and only the negative wave remained. With the ipsilateral LVN stimulation, the amplitudes of both peaks of the negative wave with the latencies of 9 msec and 14 msec decreased with the advance of the electrode, flattening at depths of 1 200 and 1 600 μ. At 3 000 μ and 4 000 μ the negative wave again reappeared, exhibiting a waveform similar to the surface potential. In this track, the unit response was not elicited by the ipsilateral LVN stimulation.

Initial triphasic and positive-negative–positive waves appeared within 3 msec after stimulation of the contralateral MVN and IVN. Since no significant changes in their phase and amplitude could be found up to the depth of 4 000 μ, the waves might be due to the afferent volleys. With MVN stimulation, the slow negative wave was seen after the initial changes. This slow negative wave, of which the peak latency was 11 msec and the amplitude was 60 μV showed hardly any variation up to a depth of 800 μ. At 1 200 μ amplitude of the negative wave was lessened and subsequently a positive deflection with the peak

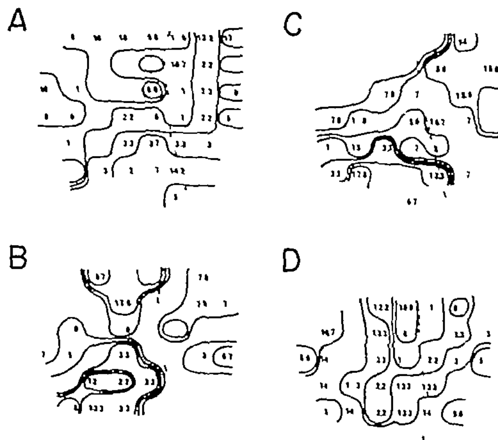


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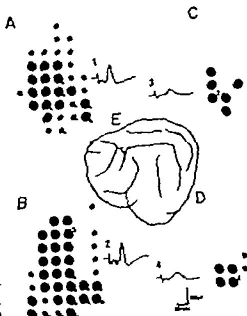


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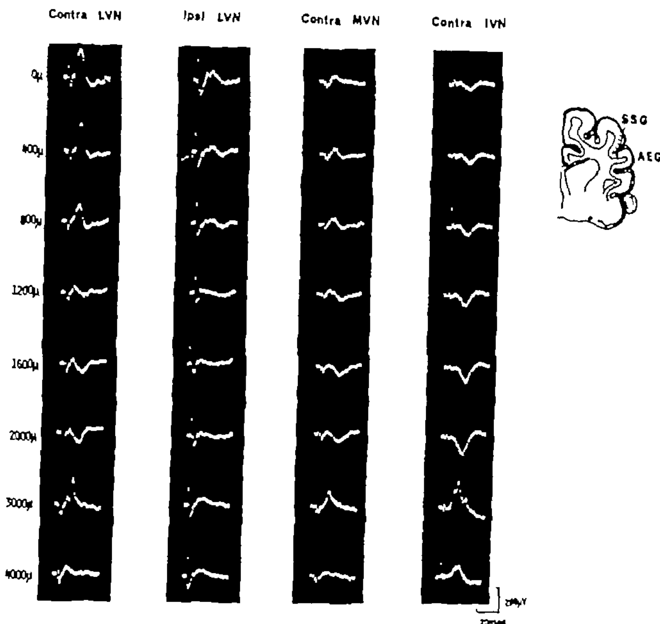


Fig 4 Depth analysis of cortical responses to electrical stimulation of the vestibular nuclei Orientation of the electrode track is shown in drawing at right of figure Note that the track passes into the neighbouring gyrus Horizontal bars drawn in the track show intervals of 1 mm.

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nuclei stimulations could make discharge to the same unit might reflect a possible convergence on the same unit from each of these nuclei.

3. *Unit Responses to Vestibular Nuclei Stimulation*

Recording of unit discharges by means of microelectrode was accomplished by five penetrations in four cats. Eleven units were responsive to vestibular stimulation, four responded to all vestibular nuclei stimulations (bilateral LVN, contralateral MVN, contralateral IVN), three units to only contralateral LVN, two units to three contralateral vestibular nuclei, one unit to the contralateral MVN and one unit to the ipsilateral LVN. During penetration, unresponsive units to the vestibular nuclei stimulation were encountered more than twice as often as the responsive units. As shown in Fig. 5, the responsive unit to all vestibular nuclei stimulations always fired on the negative wave of field potential, having latencies of 2.5 msec, 3.7 msec, 3.3 msec and 2.4 msec for stimulation of the contralateral LVN, MVN, IVN and ipsilateral LVN respectively in the first spikes. Patterns of these responding discharges were illustrated as poststimulus-time histograms (PSTH) constructed with 50 successive stimuli (Fig. 6A–D). The PSTH of the contralateral LVN had an initial peak at 4–5 msec after stimulus artifact, followed by a longlasting inhibitory phase of about 40 msec. In contrast, with the ipsilateral LVN stimulation, the PSTH was characterized by a facilitatory response, with only a very short (about 6 msec) inhibition. This fact suggests that contralateral and ipsilateral LVN had an antagonistic relationship in regard to the cortical vestibular unit. Response pattern to the stimulation of the contralateral MVN was very similar to that of LVN stimulation. With the contralateral IVN stimulation, the inhibitory phase following initial excitation was not obvious.

4. *Effects of Visual Pathway Stimulation*

The LGNd stimulation elicited spike discharges corresponding with the positive and following negative deflections of the field potential (Fig. 5F). The latencies of spike discharges were divided into two groups, 5.2 msec and 8.0 msec. Even with the former latency it was too long to postulate a direct connection between the LGNd and cortical vestibular field. There would seem to be some relay stations between them.

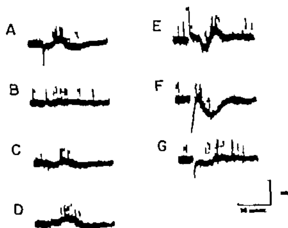


Fig. 5. An example of unitary response in the cortical vestibular field. A, C and D: contralateral LVN, MVN and IVN stimulation. B, E–G: ipsilateral LVN, LGNd, Clare-Bishop area and striate cortex stimulation respectively. All records are obtained from the same unit. Dots indicate the stimulus artifact.

Visual cortex (VC) stimulation did not elicit a distinct response (Fig. 5G) with the vestibular units examined. In the PSTH, the VC stimulation showed a slight increase of discharges at 8 to 12 msec after the stimulation. However existing only in the frequency range of spontaneous discharges, it could not definitely be attributed to VC stimulation.

5. *Effects of Visual Association Area Stimulation*

Of the eleven units responsive to the vestibular nuclei stimulations, six were also fired by the C–B stimulation. The spike discharges superimposed on the negative wave of the field potential, and had a latency varying from 1.7 msec to 5 msec, averaging 2.76±0.87 msec (mean and S.D.), as shown in Figs. 5F and 7G. In some units the initial excitation was composed of two stages which had latencies of 3.1 and 6.8 msec respectively (Fig. 7G). The excitation was

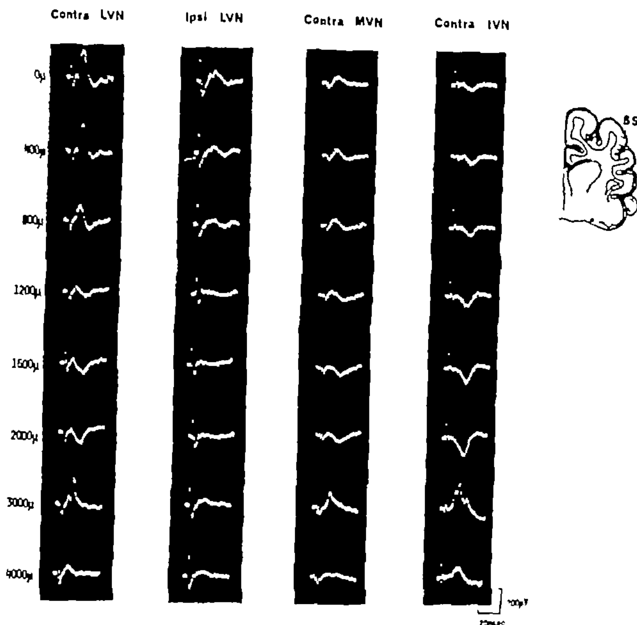


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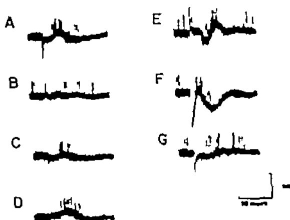


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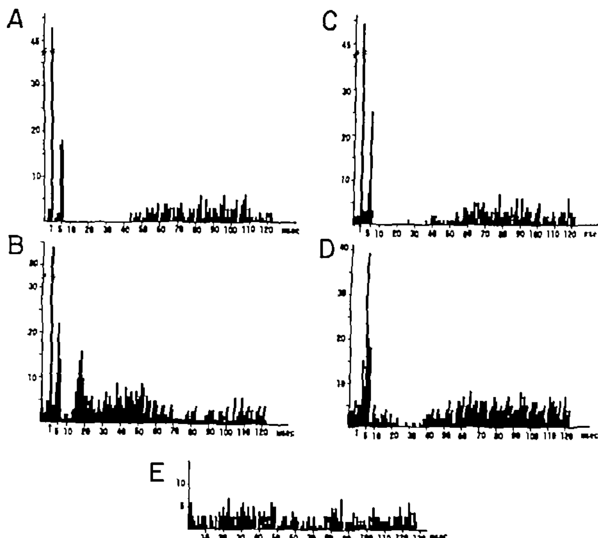


Fig 6 Post-stimulus time histogram for a unit in the vestibular cortical field responded to the electrical stimulation of vestibular nuclei. A, C and D contralateral LVN MVN and IVN stimulation B ipsilateral LVN stimulation, respectively E, spontaneous firing. Ordinate: number of firing. Abscissa time after stimulation which is indicated by arrow

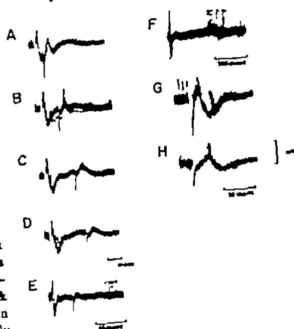
followed by a long-lasting inhibitory phase of more than 100 msec, and then a facilitatory phase or the rebound phenomena, which reached maximum at 150 msec after stimulation (Fig 7F and Fig. 8A, B) Concerning the long lasting inhibitory phase an interaction between the vestibular and the Clare–Bishop stimulations was examined, using the C–B stimulation for a conditioning shock and the contralateral LVN stimulation for a test shock. During the initial excitatory phase of about 20 msec elicited by the conditioning shock the field potential evoked by the test shock increased its amplitude up to 110% of control and the spike discharge was lasted until 25 msec. Thereafter the amplitude of field potentials evoked by the test shock decreased immediately to reach minimum at about 40 to 50 msec. The decrease in amplitude lasted about 120 msec, during which no spike discharge was elicited (Fig. 7 and Fig. 8A B).

DISCUSSION

1 *Location of cortical vestibular center*

One purpose of the present study was to resolve whether any difference exists in the projection from each of the three vestibular nuclei because Andersson & Gernandt (1954) had reported that the cortical projections from the particular end organs were revealed separate distributions

Fig. 7. Interaction between contralateral LVN and ipsilateral Clare-Bishop area stimulations. A–D: conditioning and test shocks were applied in the Clare-Bishop area and the contralateral LVN, respectively. Note the difference in time scales. F–H: control records of the responses of the same unit to the stimulation of the contralateral LVN (H), the ipsilateral Clare-Bishop area (F and G).



moreover the vestibular nerve fibers originating from each end organ were found to terminate in different vestibular nuclei (Gacek, 1969). Another aim was to confirm the extent of projection fields of the vestibular nuclei. As for the difference in projection field, there was only a slight difference with MVN and IVN but both fields were actually within that of LVN. This corroborated the data presented by Andersson & Gernandt (1954), namely that the projection field of the MVN was situated caudo-medially

Fig. 8. Post-stimulus time histogram for unit in vestibular field. A and B, Clare-Bishop area stimulation, C, ipsilateral striate cortex stimulation, D: spontaneous firing. All else as in Fig. 6.

to that of the IVN The whole extent of the cortical projection fields was consistent with the experiments involving stimulation of vestibular nerves performed by Walzl & Mountcastle (1949) Kempinsky (1951) and Mickle & Ades (1952) but findings did not agree strictly with data from stimulation of the vestibular nuclei by Massopust & Daigle (1960) which showed more ventro-caudal spreading of the fields than in the present study This latter disagreement may owe to the difference in stimulating sites as well as differing depth of anesthesia.

Concerning a dominancy of responses to either side of the vestibular nuclei most papers have indicated that the projection fields responding were principally contralateral while the extent of the fields projecting from each side were symmetrical In our experiments, this was verified except for stimulation of LVN The main area of response to the ipsilateral LVN stimulation was smaller than with the contralateral one and it inclined slightly toward the lateral part Some units on the other hand exhibited an antagonistic relationship they were facilitated by the ipsilateral LVN stimulation but inhibited by contralateral stimulation throughout the same period This suggests that the region may play a part in motor control acting as an oculomotor for example None the less, to read Kornhuber (1972) the primary vestibular projection area of the cortex does not belong to the oculomotor field as revealed by stimulation experiments Against this, our previous experiments (Miyake et al 1973) have suggested that this region also is somehow involved with eye-movements, its electrical stimulation having revealed conjugate centering. Pasik et al (1971) argued that the efferent pathways responsible for the fast phase of optokinetic nystagmus are the same as those for conjugate gaze Wood et al (1973) also pointed out that in order to impair the cortical optokinetic nystagmus cortical lesions have to involve not only the visual cortex but the wide region of the association area including the suprasylvian sulcus belt as well as the vestibular center From these further evidences, the cortical vestibular fields may also be considered to have a role in the visual regulation of eye position, as described by Kornhuber (1972)

2. *Bimodal projection in vestibular center*

According to Sanides & Hoffmann (1968), the vestibular projection area is situated in the anterior suprasylvian sulcus belt S_{aa}, and a part of the suprasylvian fringe area, SSF which is located in the suprasylvian integration belt, SSi Therefore various somatosensory auditory and visual information comes to the adjacent areas. Moreover as found by Oscarsson & Rosen (1963) and Fredrickson (1964) in the cat, and by Fredrickson et al (1966*a*) Fredrickson et al (1966*b*) and Schwarz et al (1973) in the monkey Group I muscle afferents and deep somatic afferents terminate in the vestibular field, which manifested a bimodal projection having two kinds of proprioception These two kinds of proprioception were seen to converge not only on the cortical level but also on the level of the vestibular nuclei accordingly the vestibular nuclei play a role of postural and oculomotor regulation as the lower order reflex center From the fact that the vestibular nuclei receive a bimodal sensation the question arises, as to whether the projection field responding to vestibular nuclei stimulation coincides with that of vestibular nerve stimulation or whether this field might extend over the somatosensory area. In the present experiments, mainly responding areas to vestibular nuclei stimulation were almost consistent with those responsive to vestibular nerve stimulation This fact may suggest that the cortical vestibular center possibly receives information principally vestibular in nature.

3 *Visuo-vestibular interaction*

The suprasylvian sulcus belt, which is very proximate to the vestibular cortex functions as a visual association cortex according to Clare & Bishop (1954) The C–B area was found to receive direct projection fibers mainly from the border region between areas 17 and 18, upon examination of the retinotopic organization (Shoumura, 1972 Shoumura & Itoh, 1972) moreover it connects profusely with the AMSS where exist

the gating mechanisms as reported by Dow & Dubner (1971). However the cortico-cortical projection of the vestibular fields is not yet clear. In present experiments, applying electrical stimulation to the anterior portion of the C–B area, of 11 units which responded to the vestibular stimulation, 6 reacted to the C–B stimulation. The latency of spike discharges was about 1.67 msec. If a conduction velocity is estimated as about 10 m/sec for the connecting path between the C–B area and the vestibular field, the latency is shorter enough to indicate a monosynaptic connection. Although there are the thalamo-cortical projections to the vestibular field arising from PO group, medial geniculate nucleus, pulvinar (Jones & Leavitt, 1973), and VPL (Mickle & Ades, 1954 Sans & Marty 1971), a cortico–thalamo–cortical projection may be too long to account for such a short latency of 1.67 msec. On the other hand, the stimulation of the visual cortex elicited little or no response from the vestibular field neurons. On this fact it can be considered that a focal stimulation may not produce an obvious response, provided that projection fibers did not connect directly or they terminated only sparsely.

By the LGNd stimulation, 6 units discharged with latencies of 5.2 and 8.0 msec. Such 6 units were composed of 1 unit responding only with the LGNd stimulation, 1 unit discharging both with LGNd and LVN stimulations, and 3 units with LVN, MVN IVN, C B and LGNd stimulations. Thus, half of the 6 units responsive to LGNd stimulation could also be activated with C B stimulation. This finding suggests that a pathway from the LGNd may not necessarily pass through the portion of the C B area stimulation, and points to the C B area as one very probable pathway from the LGNd.

Neuronal responses of the cortical vestibular center to the C B stimulation consisted of an initial excitation of 20 msec followed by a long-lasting inhibition as long as 120 msec. This sequence of excitation-inhibition may practise just as gate for selection of input to the vestibular center, namely visual information, which may probably be processed at the visual association area and then relayed to the vestibular center. There it serves to control the vestibular and somatosensory information to execute higher regulation of postural and oculomotor functions.

ACKNOWLEDGEMENTS

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Takashi Tokita, Tomoo Suzuki, Takaya Hibi and Tatsuku Tomita

From the Department of Otolaryngology, Gifu Medical School, Gifu, Japan

Abstract. A quantitative test of optokinetic nystagmus was proposed. Horizontal nystagmus was examined by large rotating cylinder with vertical stripes. Nystagmus responding to the cylinder rotation with an acceleration of $1°/sec^2$ for 90 seconds was recorded with an electronystagmograph. On the records, the number of beats, average eye-speed, and average amplitude per each 10 seconds were calculated. This method was suitable for testing the nature of optokinetic nystagmus which indicates the ability of the eyes to adapt to objects moving through the visual field. Moreover, in order to save trouble in hand-scoring of each parameter of nystagmus, computer processing of electronystagmographic data was introduced. The results were printed numerically on the teletypewriter and displayed graphically on a cathode ray tube and X–Y recorder. By displaying measured values on the form already printed with the normal ranges, the evaluation of the results was performed readily and objectively.

Since Bárány (1921) first introduced it into the clinical examination of hemianopsia, optokinetic nystagmus has been observed in cases with disturbance of the visual organ, labyrinth, cerebrum, cerebellum, and brain-stem by Fox & Holmes (1926), Cogan & Loeb (1949), Carmichael et al. (1954), Sato (1955), Enoksson (1956), Smith & Cogan (1959, 1960), and Smith (1963). The results of these tests were evaluated on the basis of the number of nystagmus beats, the eye-speed in the slow phase of nystagmus, amplitude, and differentiated response between right and left nystagmus. However, the evaluation of these tests has remained rather qualitative, and its quantitative evaluation is yet to be established.

Optokinetic nystagmus is an equilibrium reflex to stabilize the position of retinal images of successive objects passing through the visual field in order to obtain clear vision. Grüttner (1939), Mackensen (1954), Mackensen & Wiegmann (1959), Koike (1959), Mackensen & Uber (1960), Mackensen & Schumacher (1960), Mackensen et al. (1961), Honrubia et al. (1967), Honrubia et al. (1968), and Komatsuzaki et al. (1969), clearly described the nature of optokinetic nystagmus. The tests of optokinetic nystagmus should be performed taking account of its physiological function. Namely, the nystagmus should be observed in relation to optokinetic stimulation, and the character of nystagmus should be demonstrated in various parameters such as the number of nystagmus beats, the eye-speed of slow and rapid phase, and the amplitude. These results should then be evaluated objectively.

The purpose of the present paper is to describe (1) a method for a quantitative test of optokinetic nystagmus developed by the present authors, (2) its normal ranges, and (3) data processing by the PDP 12 computer.

METHOD

1. *Apparatus*

(1) For examination of horizontal optokinetic nystagmus, a large cylinder made of a white vinyl curtain was used. The cylinder was 2 m in diameter and 2 m in height. Along the inner surface of the cylinder, 12 vertical black stripes were drawn 5 cm in width at equal distances. A subject was placed on a chair located in the center of the cylinder with his head held in position. The

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examination was carried out for both right and left rotation of the cylinder

(2) For examination of vertical optokinetic nystagmus, a Jung type projection device was used The radius of the projection screen was 90 cm and the visual angles were 180 vertically and 60 horizontally The interval of light stripes was 30 and the width of the stripes was 3 cm A subject was seated 90 cm away from the screen with his head positioned at the center of the circle made by the screen, and upward and downward optokinetic stimuli were given

2. *Optokinetic stimulation*

(1) Examination of horizontal optokinetic nystagmus. The cylinder was rotated electrically with an angular acceleration of 2°/sec² for 90 seconds. The cylinder speed was gradually increased from 0 to 180 /sec.

(2) Examination of vertical optokinetic nystagmus. The light stripes were rotated with an angular acceleration of 1 /sec² for 90 seconds. The final rotation speed was 90°/sec.

The accelerated optokinetic stimulation was adopted to check visual adaptation to moving objects. To standardize recognition of stripes, subjects were instructed to count the stripes moving by

3 *Recording*

The nystagmus was recorded with an electronystagmograph (ENG) A ten-degree eye movement was calibrated to be equivalent to 1 cm of pen deflection of the recorder The paper speed was 1 cm/sec Time constant was set at 1 5 seconds. For the observation of the beating field of nystagmus a DC amplifier was used

4 *Parameter and measurements of optokinetic nystagmus*

The following measurements were made from the electronystagmogram.

(i) The total number of nystagmus beats for 90 seconds

Furthermore, the ENG recording for 90 seconds was divided into 9 equal parts at 10 second intervals and the following measurements were performed

(ii) The number of nystagmus beats for each 10 seconds

(iii) The average eye-speed of slow phase of nystagmus for each 10 seconds.

(iv) The average amplitude for each 10 seconds.

(v) The amplitude histogram for each 10 seconds.

The reason for calculating the average values for each 10 seconds was to observe how the occurrence of nystagmus changed with the increase of the speed of cylinder rotation The values measured from ENG record of each clinical case were plotted in each figure, the abscissa showing the time course and the ordinate indicating the number of nystagmus beats, the eye-speed of slow phase, or the amplitude. Use of figures on which the below mentioned normal ranges had already been printed, facilitated immediate evaluation of the results.

(vi) The beating field of nystagmus. The distance between the middle point of the slow phase of each nystagmus and the base line was measured on the ENG recording and the values were plotted on graph paper

NORMAL RANGES

1 *Subjects*

To determine the normal ranges, examinations were made upon two groups composed of 15 male and female subjects respectively and ranging in age from fifteen to fifty

2. *Calculation of normal ranges*

With horizontal optokinetic nystagmus, nystagmus induced by right rotation of the cylinder (left nystagmus) and nystagmus induced by left rotation of the cylinder (right nystagmus) were processed together From the measured values of 30 cases (60 sides) 95 confidence limits and rejection limits at the 5 % of level of significance of the number of beats, the eye-speed of slow component and the amplitude were calculated. In the amplitude histogram the average values were calculated The beating field of nystagmus

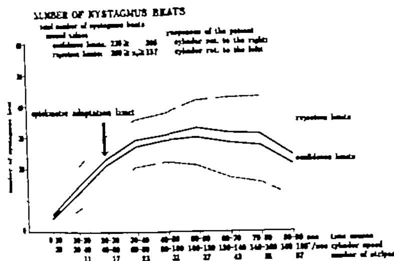


Fig 1 Normal ranges in the number of beats of the horizontal optokinetic nystagmus induced by cylinder rotation with angular acceleration of 1 /sec² for 90 seconds.

was estimated from the graphs in which measured values were plotted.

For vertical optokinetic nystagmus, since the accurate calibration of the amplitude of eye movement was often difficult, only the normal ranges in the number of nystagmus beats were calculated. Values for nystagmus induced by upward stripe rotation (downward nystagmus) and those for downward stripe rotation (upward nystagmus) were calculated separately

1. *Normal ranges of horizontal nystagmus*

(1) The total number of nystagmus beats in 90 seconds.

95 % confidence limit $220 \geq m \geq 206$
rejection limit (level of significance = 5 %)
$269 \geq x_0 \geq 157$

(2) The number of nystagmus beats for each 10 seconds. Fig. 1 shows confidence limits and rejection limits for each 10 seconds. The number of beats increases proportionally with the speed of cylinder rotation up to 40–60°/sec. But as cylinder speed increases beyond this range, the increase in the number of beats is proportionately less, and the number of beats actually decreases when the cylinder speed exceeds 100°–120°/sec. The upper limit of the linear increase in

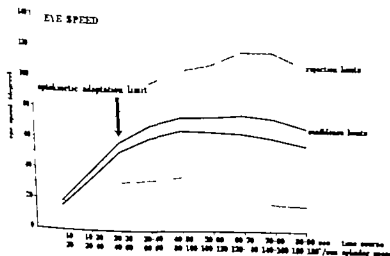


Fig 2. Normal ranges in the eye-speed of slow phase of the horizontal optokinetic nystagmus.

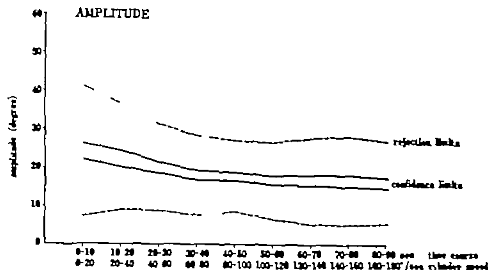


Fig 3 Normal ranges in the amplitude of the horizontal optokinetic nystagmus.

beats (indicated with an arrow) is the limit of visual fixation to objects passing through the visual field (optokinetic adaptation limit)

(3) The average eye-speed of slow phase of nystagmus for each 10 seconds Fig. 2 shows the confidence and rejection limits for average eye speed of slow phase in nystagmus for each 10 seconds. The speed of cylinder rotation and the eye-speed are the same until the cylinder speed reaches up to 40 –60°/sec. But as cylinder speed increases beyond this range the increase in the eye-speed is proportionately less. The upper limit where the cylinder speed and the eye-speed are still the same (indicated with an arrow in the figure) is the optokinetic adaptation limit.

(4) The average amplitude for each 10 seconds. The confidence limits and rejection limits of the average amplitude for each 10 seconds are shown in Fig. 3 As the speed of cylinder rota tion increases, the amplitude becomes smaller

(5) The amplitude histogram for each 10 seconds. Fig. 4 shows the histogram of amplitude in each interval of 10 seconds. When the speed of cylinder rotation remained low nystagmic amplitudes were observed in all the ranges of 0°–10° 10°–20° 20 –30 and over 30° As the rotation speed increased, the amplitude in the range of 20 –30° became more frequent, and that of 10 –20° became more pronounced in much higher cylinder speeds.

(6) The beating field of nystagmus. Fig. 5 indicates the beating field of nystagmus in a

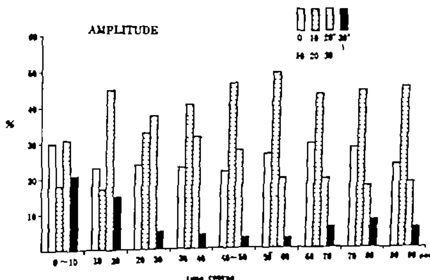


Fig 4 Amplitude histogram of the horizontal optokinetic nystagmus (mean values).

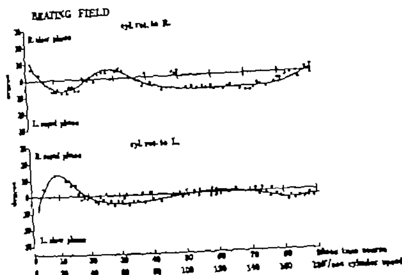


Fig. 5. Beating field of the horizontal optokinetic nystagmus in normal subject.

normal subject. Although at the onset of stimulation the beating field is found on the side of the slow phase, as the stimulation continues it immediately shifts to that of the rapid phase. When the speed of cylinder rotation exceeds 40°/sec, it shifts back to the slow phase side and then it stays near the base line despite the further increase of stimulation. This shifting pattern of the beating field is most commonly observed among normal subjects.

4. *Normal ranges of vertical nystagmus*

(1) The total number of nystagmus beats in 90 seconds.

Downward rotation (upward nystagmus)

95 confidence limit $152 \geq m \geq 129$

rejection limit (level of significance = 5 %)

$204 \geq x_0 \geq 76$

Upward rotation (downward nystagmus)

95 % confidence limit $140 \geq m \geq 1\ 4$

rejection limit (level of significance = 5 %)

$179 \geq x_0 \geq 85$

(2) The number of nystagmus beats per 10 seconds. In vertical nystagmus, both upward and downward nystagmus show less increase in the number of beats when the speed of light stripes 20°/sec. The result demonstrates that the optokinetic adaptation limit for vertical optokinetic stimuli is less than for horizontal optokinetic stimuli.

DATA PROCESSING BY COMPUTER

1. *Equipment*

The optokinetic nystagmus was recorded on a magnetic tape together with recording by a pen oscillograph using an electronystagmograph. The nystagmographic data were analyzed with a PDP 12 computer (DEC) consisting of a central processing unit (4096 word core memory), analog to digital converter LINC tape system, cathode ray tube display system, teletype unit, and X–Y recorder. The following computer program, OKNYST has been developed for the data processing in a quantitative test of optokinetic nystagmus.

2. *Program (OKNYST)*

The program was written in an assembly language (LINC and 8 mode instructions). The autoprocessing of nystagmographic data was performed as follows

(1) Chart number name, sex, age, date, direction of cylinder rotation, sampling interval, and average time were asked on the teletypewriter

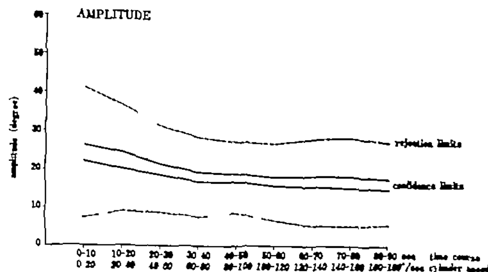


Fig 3. Normal ranges in the amplitude of the horizontal optokinetic nystagmus.

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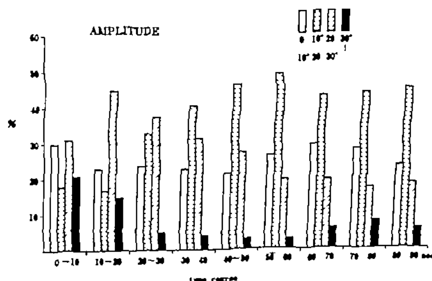


Fig 4 Amplitude histogram of the horizontal optokinetic nystagmus (mean values).

Fig. 7. Teletypewriter printout of the eye-speed of rapid phase of the horizontal optokinetic nystagmus in a normal subject.

low and rapid phases, etc. could be printed on the teletypewriter.

3. *Results*

The optokinetic nystagmus of 30 normal subjects was measured using the PDP 12 computer. With the measured values, 95% confidence limits and rejection limits at 5% of level of significance were calculated for number of beats, eye-speed, and amplitude. When these results were compared with those obtained from hand scoring, the confidence and rejection limits had narrower ranges. This was probably due to the small dispersion of measured values.

DISCUSSION

1. *Significance of the examination of optokinetic nystagmus*

(i) The physiological function of nystagmus is to stabilize the position of retinal images of objects moving through the visual field in order to obtain clear vision. Therefore, optokinetic nystagmus is an equilibrium reflex of the eyes and its examination tests the primary function of nystagmus. On the other hand, the examination of induced labyrinthine nystagmus is a test of nystagmus without the function maintaining visual fixation to the moving objects. In the examination of nystagmus, the test of both kinds of nystagmus, which differ in their physiological significance, is useful to explain the peculiar characteristics of nystagmic abnormalities.

(ii) Optokinetic nystagmus is a reflex mediated through the retina, superior colliculus, lateral geniculate body, striate cortex, brain-stem, and oculomotor nuclei. This reflex is modified by the cerebrum, cerebellum, basal gangila, and reticular formation of the brain-stem. Therefore, the examination of optokinetic nystagmus is effective to check any central vertigo and equilibrium disturbance.

(iii) Since the appearance of optokinetic nystagmus indicates the ability of the eyes to adapt to objects moving through the visual

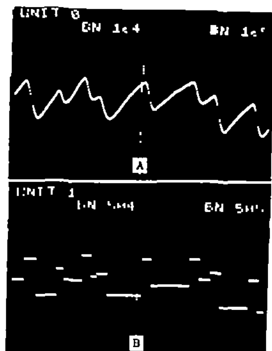


Fig 6. Nystagmus processing by OKNYST program. (A) Nystagmographic data from the magnetic tape are con verted by analog to digital converter sampled at intervals of 5 msec, and stored in the LINC tape as shown. (B) From the stored data, A, the difference between two successive sampled values was computed and the polarities of the difference were examined. While the polarities were same the values examined were changed into the value of the last point at which the polarity changed. The results stored again in the LINC tape showing in the figure.

in this sequence. The answers to the questions were given by teletypewriter

(2) The nystagmographic data (analog signals) from the magnetic tape were converted to series of digital numbers with 10 bit conversion range (−511 to +511) by the analog to digital converter Since the input range of the PDP 12 is ±1 V by calibrating the eye movement with an amplitude of ±30 equivalent to ±0 47 V 1 of eye movement was converted to 8 in digital numbers. The sampling interval was determined by a real time clock. In the program used the sampling intervals were selected from 5 10 and 20 msec. The data were stored in the LINC tape (Fig. 6A)

(3) From the stored data, the peak and valley of nystagmus wave were determined, e g. the difference between two successive sample values were computed. First of all the polarities of the differences were examined and the change of polarities between the two data points was sidered to indicate either a peak or valley 6B) When the difference of the values fo possible peak and valley was less than 3 were eliminated as a noise When two or peaks were found within 100 msec, the la was considered as a peak and the smallest valley Further when a change of more 150°/sec was observed in a slow phase, it regarded as an abnormal wave and was correc

(4) Using peak and valley values determine the previous manner the eye speed of slow rapid phase and amplitude of each nystag was computed.

(5) The results were displayed in the follov manner

3 *Display*

(1) Teletypewriter printout

(i) Chart number name sex, age, date, direction of cylinder rotation

(ii) The number of beats for 90 seconds for each 10 seconds.

(iii) The individual and average eye-speed slow phase for each 10 seconds.

(iv) The individual and average eye-speed rapid phase for each 10 seconds (Fig. 7).

(v) The average and histogram of amplitu in each 10 seconds (Fig. 8)

(2) Display on the cathode ray tube T cathode ray tube graphically displayed succe sively the number of beats, average eye-speed slow phase, average eye-speed of rapid phas and average amplitude in each 10 seconds. Tin was plotted on the abscissa and measured valu on the ordinate (Fig. 9).

(3) Display on the X–Y recorder The X–Y recorder can graphically display the same item as the cathode ray tube. The abnormality an its nature were easily identified by displaying th measured values on graph paper on which th normal ranges had previously been printed such as Figs. 1 2, and 3

(4) In addition to the displays mentioned above, the values at any processing step could be dumped optionally i.e. sampled values, the respective peak and valley values, durations of

Fig. 7. Teletypewriter printout of the eye-speed of rapid phase of the horizontal optokinetic nystagmus in normal subject.

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DISCUSSION

1. *Significance of the examination of optokinetic nystagmus*

(i) The physiological function of nystagmus is to stabilize the position of retinal images of objects moving through the visual field in order to obtain clear vision. Therefore, optokinetic nystagmus is an equilibrium reflex of the eyes and its examination tests the primary function of nystagmus. On the other hand, the examination of induced labyrinthine nystagmus is a test of nystagmus without the function maintaining visual fixation to the moving objects. In the examination of nystagmus, the test of both kinds of nystagmus, which differ in their physiological significance, is useful to explain the peculiar characteristics of nystagmic abnormalities.

(ii) Optokinetic nystagmus is a reflex mediated through the retina, superior colliculus, lateral geniculate body, striate cortex, brain-stem, and oculomotor nuclei. This reflex is modified by the cerebrum, cerebellum, basal ganglia, and reticular formation of the brain-stem. Therefore, the examination of optokinetic nystagmus is effective to check any central vertigo and equilibrium disturbance.

(iii) Since the appearance of optokinetic nystagmus indicates the ability of the eyes to adapt to objects moving through the visual

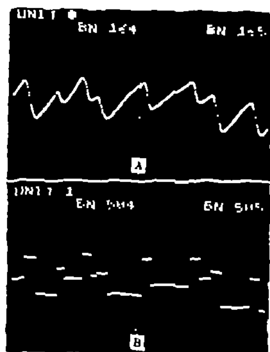


Fig 6 Nystagmus processing by OKNYST program. (A) Nystagmographic data from the magnetic tape are converted by analog to digital converter sampled at intervals of 5 msec, and stored in the LINC tape as shown. (B) From the stored data, A, the difference between two successive sampled values was computed and the polarities of the difference were examined. While the polarities were same, the values examined were changed into the value of the last point at which the polarity changed. The results stored again in the LINC tape showing in the figure.

in this sequence The answers to the questions were given by teletypewriter

(2) The nystagmographic data (analog signals) from the magnetic tape were converted to series of digital numbers with 10 bit conversion range (−511 to +511) by the analog to digital converter Since the input range of the PDP 12 is ±1 V by calibrating the eye movement with an amplitude of ±30 equivalent to ±0 47 V 1 of eye movement was converted to 8 in digital numbers. The sampling interval was determined by a real time clock In the program used, the sampling intervals were selected from 5 10 and 20 msec. The data were stored in the LINC tape (Fig. 6A).

(3) From the stored data, the peak and valley of nystagmus wave were determined e.g., the difference between two successive sample values were computed. First of all, the polarities of the differences were examined and the change of polarities between the two data points was considered to indicate either a peak or valley (Fig. 6B) When the difference of the values for the possible peak and valley was less than 3 they were eliminated as a noise. When two or more peaks were found within 100 msec, the largest was considered as a peak and the smallest as a valley Further when a change of more than 150 /sec was observed in a slow phase, it was regarded as an abnormal wave and was corrected.

(4) Using peak and valley values determined in the previous manner the eye-speed of slow and rapid phase and amplitude of each nystagmus was computed.

(5) The results were displayed in the following manner

3 *Display*

(1) Teletypewriter printout

(i) Chart number name, sex, age, date, and direction of cylinder rotation

(ii) The number of beats for 90 seconds and for each 10 seconds.

(iii) The individual and average eye-speed of slow phase for each 10 seconds.

(iv) The individual and average eye-speed of rapid phase for each 10 seconds (Fig. 7).

(v) The average and histogram of amplitude in each 10 seconds (Fig. 8).

(2) Display on the cathode ray tube The cathode ray tube graphically displayed successively the number of beats, average eye-speed of slow phase average eye-speed of rapid phase, and average amplitude in each 10 seconds. Time was plotted on the abscissa and measured values on the ordinate (Fig. 9).

(3) Display on the X–Y recorder The X–Y recorder can graphically display the same items as the cathode ray tube. The abnormality and its nature were easily identified by displaying the measured values on graph paper on which the normal ranges had previously been printed such as Figs. 1 2, and 3

(4) In addition to the displays mentioned above, the values at any processing step could be dumped optionally i.e., sampled values, the respective peak and valley values, durations of

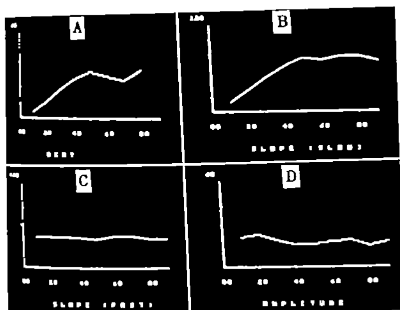


Fig. 9. Cathode ray tube display of the horizontal optokinetic nystagmus in normal subject. (A) Number of beats for each 10 seconds. (B) Average eye-speed of slow phase for each 10 seconds. (C) Average eye-speed of rapid phase for each 10 seconds. (D) Average amplitude for each 10 seconds.

and total eyeball velocity over any selected number of seconds and an analog display of the eye position and velocity on a cathode ray tube. Herbert et al. (1968), using a Swedish Datasaab D21 computer with programs coded in Algol, presented (*a*) differentiated response under correction for spontaneous nystagmus, (*b*) total amplitude, (*c*) total number of beats within different phases of the recording, (*d*) duration of each phase, (*e*) occurrence in time of maximum response and its size, and (*f*) maximum frequency in caloric nystagmus. The results were printed numerically and the differentiated responses were graphically displayed on a line printer. Tole and Young (1971) used hybrid equipment consisting of a Digital Equipment PDP-8 digital computer connected to a GSP 290T analog computer and calculated cumulative slow phase position and slow phase velocity in vestibular nystagmus and optokinetic nystagmus. Matz et al. (1970) calculated the number of nystagmus beats and the total eye displacement in the rapid phase of caloric nystagmus for every 5 seconds with an analog computer and printed them on an X–Y plotter.

In performing the quantitative test of optokinetic nystagmus, using a PDP 12 computer with a program (OKNYST coded in assembly language), the authors calculated the number of beats, eye-speed of slow and rapid phase, and amplitude. This procedure offered the following advantages. (i) Computer analysis slashed the time usually necessary for manually performing the measurements and processing of nystagmus. (ii) By numerically printing out the measured values on the teletypewriter and displaying them on the cathode ray tube and X–Y recorder the evaluation of the results was done readily and objectively.

However problems in the recognition of abnormal wave forms, and auto-diagnosis remain to be solved.

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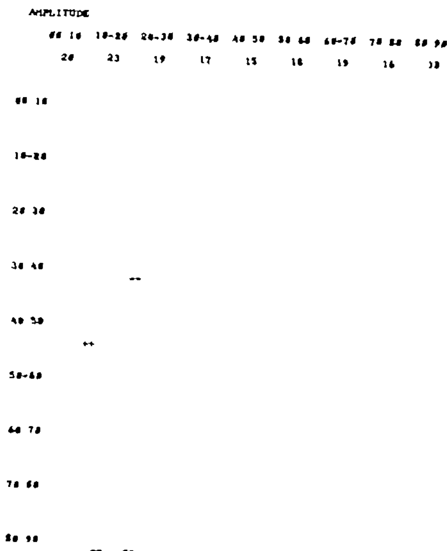


Fig 8. Teletypewriter printout of the amplitude of the horizontal optokinetic nystagmus in a normal subject.

field the *superior eye function of a ball player* or the disturbance of visual fixation function of a drunken person may be demonstrated objectively by the examination of optokinetic nystagmus.

2. Merits of the quantitative test of optokinetic nystagmus

(i) By using the cylinder rotation with angular acceleration of 1°/sec² for 90 seconds as optokinetic stimulation, it is possible to continuously observe visual adaptation to moving objects (stripes) with gradually increased speed from 0 to 180°/sec. Especially the optokinetic adaptation limit can be observed

(ii) By quantitative comparison of the values obtained by testing clinical cases with the normal ranges, the results are evaluated easily and objectively

(iii) Since the number of beats, eye-speed, and amplitude of optokinetic nystagmus are examined, the degree and character of nystagmic abnormality can be better demonstrated.

Despite the fact that the quantitative test described above has many merits, it requires time-consuming work, which is why the computer processing of nystagmographic data has been developed.

3 Computer processing of nystagmographic data

Using a specially designed computer Johnson et al. (1967) presented a digital readout of the average eyeball velocity of the preceding second

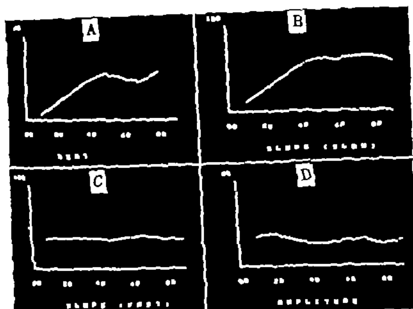


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OPTIC ORGAN AND CERVICAL PROPRIOCEPTORS IN MAINTENANCE OF BODY EQUILIBRIUM

Manabi Hinoki, Sonoji Hine, Shuji Okada, Yoshio Ishida, Satoshi Koike and Shunichi Shizuku

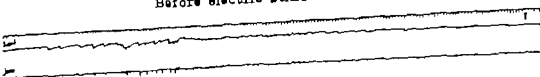
From the Department of Otolaryngology School of Medicine, Tokushima University Tokushima, Japan

Abstract. Two experiments were made on the functional correlation between the optic organ and the cervical proprioceptors in maintenance of body equilibrium. Experiment I. The effects of weak and strong electric stimulation of the deep nuchal muscles on changes in optokinetic nystagmus and optokinetic after-nystagmus were compared in adult non-albino rabbits with binocular vision. Experiment II. Experiment I was repeated on rabbits with monocular vision giving optokinetic stimulation moving from the side of the blindfolded eye to that of the open eye and applying only weak electric stimulation to the neck muscles. The results obtained were as follows: (1) Experiment I. Weak electric stimulation of the deep nuchal muscles of rabbits with binocular vision tended to promote optokinetic nystagmus with either no significant change or decrease in optokinetic after-nystagmus. Strong electric stimulation had the opposite effects, it tended to inhibit optokinetic nystagmus and activate optokinetic after-nystagmus. It also produced abnormal optokinetic nystagmus, such as the inversion phenomenon of optokinetic nystagmus and optokinetic nystagmus firing. (2) Experiment II. Weak electric stimulation of the deep nuchal muscles of rabbits with monocular vision had similar effects to those in experiment I, but promotion of optokinetic nystagmus was less obvious, this activation of optokinetic after-nystagmus was more marked. In addition, the inversion phenomenon of optokinetic nystagmus developed even on weak electric stimulation. From these results the following conclusions were drawn. (1) The cervical proprioceptors can function as two mechanisms causing promotion and break down of equilibrium of the optokinetic system. (2) The cervical proprioceptors, as an organ of equilibrium, can exert two different actions on the optokinetic eye reflexes, i.e., they can promote optokinetic nystagmus and inhibit optokinetic after-nystagmus.

It is generally accepted that there is a close relationship between the optic organ and the labyrinth in maintenance of body equilibrium. For instance Fukuda, Hinoki and Tokita found that when an adequate labyrinthine stimulus was given to rabbits at the same time as an optokinetic stimulus, the animals showed increased adaptability to optokinetic stimulation and responded well to environmental changes that were too rapid for reaction of the optic organ alone (Fukuda et al., 1957). It seems possible that there is a similar relationship between the optic organ and the cervical proprioceptors in maintenance of body equilibrium. For instance, Hinoki & Terayama reported that when procaine, which blocks the activity of gamma fibers and consequently inhibits the function of the proprioceptors, was injected into the deep nuchal muscles of guinea pigs, development of optokinetic head and eye nystagmus was strongly inhibited (Hinoki & Terayama, 1966). Furthermore, we found that optokinetic nystagmus was inactive in many vertigo cases with whiplash injury who complained of neck pain and showed abnormal EMG's from the neck region, and that when the neck of these patients was fixed with a collar optokinetic nystagmus developed actively in parallel with reduction in the abnormal EMG's (Hinoki et al., 1971).

To test the validity of this idea in more detail, it seems necessary to determine whether changes in optokinetic reflexes are parallel with the intensity of stimuli given to the cervical proprioceptors in man and animals. No systematic experimental studies have yet been made on this.

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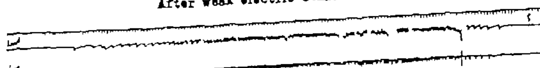


Fig. 1. Optokinetic nystagmus and optokinetic after-nystagmus before and after weak electric stimulation of the deep nuchal muscles of rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well while the velocity of cylinder rotation was low and optokinetic stimuli were enough for the optic organ. However when the velocity of cylinder rotation increased, this nystagmus decreased in frequency and amplitude. After weak electric stimulation, nystagmic responses increased appreciably so that the velocity of cylinder rotation giving the maximum frequency of nystagmus increased. No optokinetic after-nystagmus was seen before or after electric stimulation.

nystagmus before and after weak electric stimulation of the deep nuchal muscles of another rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus of small or medium amplitude developed to the left, but it was inactive during optokinetic stimulation. Five jerks of optokinetic nystagmus were observed in 180 seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20°/sec. Optokinetic after-nystagmus of medium amplitude developed to the right and showed 7 jerks. The ENG at the bottom of this figure shows optokinetic nystagmus and optokinetic after nystagmus after electric stimulation. Again nystagmus increased appreciably optokinetic nystagmus to 27 jerks in 180 seconds and the velocity of cylinder rotation giving the maximum frequency of nystagmus to between 21°/sec and 40°/sec. One jerk of optokinetic after nystagmus was seen to the right.

2. *Results in other animals.* Table I shows results of weak electric stimulation of the neck muscles in 8 other rabbits. Electric stimulation increased the total number of nystagmic jerks in 6 of the 8 animals and raised the velocity of cylinder rotation giving the maximum frequency of nystagmus in all of these 6 animals. However it reduced the frequency of nystagmic jerks in 2 rabbits and in one of these it decreased the velocity of cylinder rotation giving the maximum frequency of nystagmus.

Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by weak electric stimulation of the neck muscles were as follows. Six of the 8 rabbits showed increased optokinetic nystagmus, with and without decrease in optokinetic after nystagmus. Incidentally only 2 of these 6 rabbits showed optokinetic after-nystagmus before electric stimulation. Two of the 8 rabbits showed inhibition of optokinetic nystagmus with no sign of development of optokinetic after nystagmus. Moreover after weak electric stimulation, 3 rabbits showed abolition of the inversion phenomenon of optokinetic nystagmus in parallel with promotion of this nystagmus.

(b) Strong electric stimulation of the neck muscles

1. *Representative cases.* Rabbit No. 11. Fig. 3 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Be-

EXPERIMENTAL

1 *Method of Electric Stimulation of the Neck Muscles*

We applied two kinds of electric stimuli one was 10 msec 10 Hz pulse waves, at 1 volt for 90 seconds (named here a weak electric stimulus) and the other was 10 msec 10 Hz pulse waves at 15 volts for 90 seconds (named a strong electric stimulus) We applied these stimuli to the deep nuchal muscles of rabbits through anodic and cathodic needle electrodes. These electrodes were inserted into the middle of the deep nuchal muscles at the level of the 2nd cervical vertebra, the anodic needle 1 cm above the cathodic one

2. *Optokinetic Stimulus and Experimental Animals*

To produce an optokinetic stimulus the optic cylinder described by Fukuda et al. was used (Fukuda et al. 1957) This is a hollow cylinder 2 m in diameter and 1 9 m in height hung from the ceiling. It was covered with white cloth with 16 black vertical stripes 4 cm wide, at equal distances apart on the inner surface. It was rotated with an angular acceleration of 1°/sec² from zero to a maximum of 180°/sec Adult non-albino rabbits were used in this experiment Their head trunk and limbs were fixed in an animal holder and then they were given the optokinetic stimulation described above

In experiment I rabbits with binocular vision were given an optokinetic stimulus produced by clockwise rotation of the optic cylinder In experiment II rabbits with monocular vision were given an optokinetic stimulus by rotation in the direction from the blindfolded eye to the open eye

3 *Estimation of the Effects of Electric Stimulation of the Neck Muscles on Development of Optokinetic Eye Reflexes*

To evaluate the effects of electric stimulation of the neck muscles on the development of optokinetic eye reflexes, we first made ENG recordings of optokinetic nystagmus and optokinetic after nystagmus before and after electric stimulation and compared the results.

To study changes in optokinetic nystagmus recorded by the ENG in more detail, the period during which the optic cylinder was rotated from zero to a maximum of 180°/sec was divided into 9 sub-periods, and the number of jerks of nystagmus in each sub-period was counted to determine the velocity of cylinder rotation giving the maximum frequency of nystagmus.

Optokinetic after nystagmus was recorded in a dark room. This nystagmus was divided into two types. In the first type optokinetic after nystagmus jerks are in the same direction as those of optokinetic nystagmus, while in the second type they are in the opposite direction.

4 *Results*

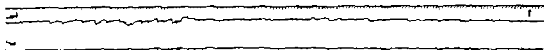
(i) EXPERIMENT I

(a) Weak electric stimulation of the neck muscles

1 *Representative cases* Rabbit No 1 Fig. 1 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after weak electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation optokinetic nystagmus of medium amplitude developed to the left. However it decreased in frequency and amplitude as the velocity of cylinder rotation increased and a total of 48 jerks were observed in 180 seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 81°/sec and 100°/sec The ENG at the bottom of Fig. 1 shows optokinetic nystagmus and optokinetic after nystagmus following electric stimulation Electric stimulation increased the response significantly A total of 135 jerks were recorded in 180 seconds and the velocity of cylinder rotation giving the maximum frequency of nystagmus was between 121°/sec and 140°/sec No optokinetic after nystagmus was seen before or after electric stimulation.

Rabbit No 2 Fig. 2 shows recordings of optokinetic nystagmus and optokinetic after

Before electric stimulation



After weak electric stimulation

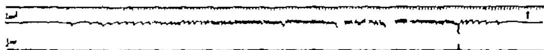


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nystagmus before and after weak electric stimulation of the deep nuchal muscles of another rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus of small or medium amplitude developed to the left, but it was *inactive during optokinetic* stimulation. Five jerks of optokinetic nystagmus were observed in 180 seconds. The velocity of cylinder rotation giving the maximum *frequency* of nystagmus was between 0° and 20°/sec. Optokinetic *after*-nystagmus of medium amplitude developed to the right and showed 7 jerks. The ENG at the bottom of this figure shows optokinetic nystagmus and *optokinetic after* nystagmus after electric stimulation. Again nystagmus increased appreciably: optokinetic nystagmus to 27 jerks in 180 seconds and the velocity of cylinder rotation giving the maximum frequency of nystagmus *to between 21 /sec and* 40 sec. One jerk of optokinetic after-nystagmus was seen to the right.

2. *Results in other animals.* Table 1 shows results of weak electric stimulation of the neck muscles in 8 other rabbits. Electric *stimulation* increased the total number of nystagmic jerks in 6 of the 8 *animals* and raised the velocity of cylinder rotation giving the maximum frequency of nystagmus in all of these 6 animals. However *it reduced the frequency of nystagmic jerks in 2* rabbits and in one of these it decreased the velocity *of cylinder rotation giving the maximum* frequency of nystagmus.

Results on changes in the relationship between optokinetic *nystagmus and optokinetic after* nystagmus caused by weak electric stimulation of the neck muscles were as follows. Six of the *8 rabbits showed increased optokinetic nystagmus*, with and without decrease in optokinetic after nystagmus. Incidentally only 2 of these 6 rabbits showed *optokinetic after nystagmus* before electric stimulation. Two of the 8 rabbits *showed* inhibition of optokinetic nystagmus with no sign of development of *optokinetic after* nystagmus. Moreover after weak electric stimulation, 3 rabbits showed abolition of the *inversion* phenomenon of optokinetic nystagmus *in* parallel with promotion of this nystagmus.

(b) Strong electric stimulation of the neck muscles

1. *Representative cases.* Rabbit No. 11. Fig. 3 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after *strong electric stimulation* of the deep nuchal muscles of a rabbit with binocular vision. Be

EXPERIMENTAL

1 *Method of Electric Stimulation of the Neck Muscles*

We applied two kinds of electric stimuli one was 10 msec 10 Hz pulse waves, at 1 volt for 90 seconds (named here a weak electric stimulus) and the other was 10 msec 10 Hz pulse waves, at 15 volts for 90 seconds (named a strong electric stimulus) We applied these stimuli to the deep nuchal muscles of rabbits through anodic and cathodic needle electrodes. These electrodes were inserted into the middle of the deep nuchal muscles at the level of the 2nd cervical vertebra, the anodic needle 1 cm above the cathodic one

2. *Optokinetic Stimulus and Experimental Animals*

To produce an optokinetic stimulus the optic cylinder described by Fukuda et al was used (Fukuda et al 1957) This is a hollow cylinder 2 m in diameter and 1 9 m in height hung from the ceiling. It was covered with white cloth with 16 black vertical stripes, 4 cm wide at equal distances apart on the inner surface It was rotated with an angular acceleration of 1 /sec² from zero to a maximum of 180°/sec Adult non albino rabbits were used in this experiment. Their head trunk and limbs were fixed in an animal holder and then they were given the optokinetic stimulation described above.

In experiment I rabbits with binocular vision were given an optokinetic stimulus produced by clockwise rotation of the optic cylinder In experiment II rabbits with monocular vision were given an optokinetic stimulus by rotation in the direction from the blindfolded eye to the open eye

3 *Estimation of the Effects of Electric Stimulation of the Neck Muscles on Development of Optokinetic Eye Reflexes*

To evaluate the effects of electric stimulation of the neck muscles on the development of optokinetic eye reflexes, we first made ENG recordings of optokinetic nystagmus and optokinetic after nystagmus before and after electric stimulation and compared the results.

To study changes in optokinetic nystagmus recorded by the ENG in more detail the period during which the optic cylinder was rotated from zero to a maximum of 180°/sec was divided into 9 sub-periods, and the number of jerks of nystagmus in each sub-period was counted to determine the velocity of cylinder rotation giving the maximum frequency of nystagmus.

Optokinetic after nystagmus was recorded in a dark room. This nystagmus was divided into two types. In the first type optokinetic after nystagmus jerks are in the same direction as those of optokinetic nystagmus, while in the second type they are in the opposite direction

4 *Results*

(i) EXPERIMENT I

(a) Weak electric stimulation of the neck muscles

1 *Representative cases* Rabbit No 1 Fig. 1 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after weak electric stimulation of the deep nuchal muscles of a rabbit with binocular vision Before electric stimulation optokinetic nystagmus of medium amplitude developed to the left. However it decreased in frequency and amplitude as the velocity of cylinder rotation increased and a total of 48 jerks were observed in 180 seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 81 /sec and 100°/sec. The ENG at the bottom of Fig. 1 shows optokinetic nystagmus and optokinetic after nystagmus following electric stimulation. Electric stimulation increased the response significantly A total of 135 jerks were recorded in 180 seconds and the velocity of cylinder rotation giving the maximum frequency of nystagmus was between 121 /sec and 140°/sec. No optokinetic after nystagmus was seen before or after electric stimulation.

Rabbit No 2 Fig. 2 shows recordings of optokinetic nystagmus and optokinetic after

Table I. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by weak electric stimulation of the neck muscles of rabbits with binocular vision*

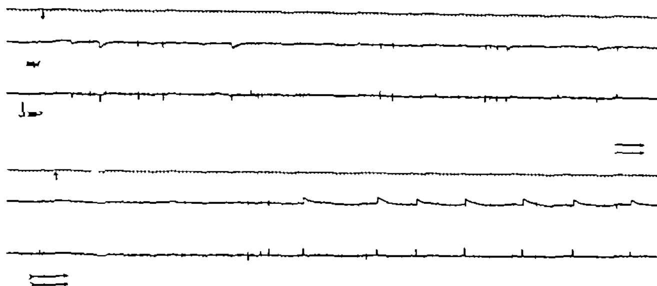
Case	Stimulation	Optokinetic nystagmus: 0°–20°	21–40°	41–60°	61–80°	81–100	101–120°	121–140°	141–160°	161–180°	Total nystagmus jerks	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after-nystagmus: 1st type	2nd type	Total nystagmus jerks
3	Before stimulation	2	2	4	2	3	2	1	0	0	16	41°–60°	0	0	0
	After stimulation	2	4	3	2	1	0	1	0	0	13	21°–40°	0	0	0
4	Before stimulation	1	5	3	7	11	25	19	11	4	86	100°–120°	0	0	0
	After stimulation	0	3	6	9	12	16	12	4	1	63	101–120	0	0	0
5 \	Before stimulation	0	2	1	1	1	0	1	1	0	7	21 40°	0	0	0
	After stimulation	0	4	3	5	6	8	4	2	1	33	100°–120°	0	0	0
6 \	Before stimulation	2	1	0	0	1	0	1	0	0	5	0°–20°	1	0	1
	After stimulation	3	1	4	2	0	0	0	1	0	11	41 60	0	0	0
7 \	Before stimulation	1	2	2	2	2	1	1	0	1	12	21°–40	0	0	0
	After stimulation	1	3		5		2	1	2	1	15	41°–60	0	0	0
8 \	Before stimulation	1	0	0	0	0	0	0	0	1		0 20	0	0	0
	After stimulation	1	2	2	4	3	1	1	2	0	16	41°–60	0	0	0
9 \	Before stimulation	1	0	0	0	0	0	1	0	0	2	0 20	0	0	0
	After stimulation	1	1	2	1	2	0	0	0	1	8	41°–60	0	0	0
10 \	Before stimulation	2	1	1	1	0	0	0	0	0	5	0 20	2	0	2
	After stimulation	2	2	3	0	1	0	1	0	0	9	41 60°	0	0	0

\ Inverted optokinetic nystagmus

Optokinetic after-nystagmus developed to the right and showed 2 jerks.

Rabbit No. 12. Fig. 4 shows recordings of optokinetic nystagmus and optokinetic after-nystagmus before and after strong electric stimulation of the neck muscles of another rabbit with binocular vision. Before electric stimulation, the animal developed inactive optokinetic nystagmus showing 7 jerks of optokinetic nystagmus in 180 seconds and the maximum frequency of nystagmus at a velocity of cylinder rotation of between 0° and 20°/sec. Optokinetic after-nystagmus of medium amplitude occurred to the right and showed one jerk. The ENG at the bottom of this figure shows optokinetic nystagmus and optokinetic after nystagmus following electric stimulation. The animal developed optokinetic nystagmus of small amplitude to the left when the velocity of cylinder rotation was low, but at increased velocity nystagmus to the left disappeared and the inversion phenomenon appeared. Thus, 20 jerks of optokinetic nystagmus were recorded, 11 to the left and 9 to the right (i.e., inverted optokinetic nystagmus). The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20°/sec. Optokinetic after-nystagmus developed to the right and showed 13 jerks.

Rabbit No. 13. Fig. 5 shows recordings of optokinetic nystagmus and optokinetic after-nystagmus before and after strong electric stimulation of the deep nuchal muscles of another rabbit with binocular vision. Before electric stimulation, the animal developed fairly active optokinetic nystagmus showing 29 jerks in 180 seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20°/sec. No optokinetic after-nystagmus was observed. After electric stimulation (ENG at bottom of Fig. 5) responses increased markedly to 237 jerks of optokinetic



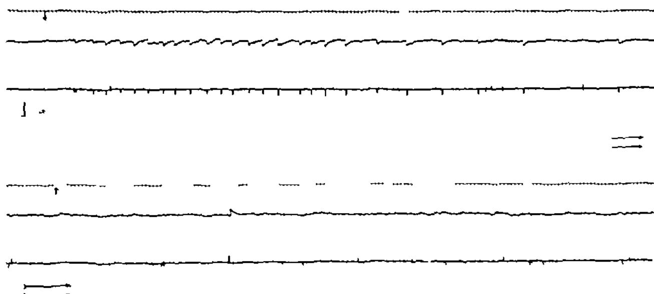


Fig 2 Optokinetic nystagmus and optokinetic after nystagmus before and after weak electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus was inactive, with fairly active optokinetic after-nystagmus. After weak electric stimulation, nystagmic responses increased, so that the velocity of cylinder rotation giving the maximum frequency of nystagmus increased. Furthermore, optokinetic after-nystagmus decreased appreciably and showed one jerk

fore electric stimulation, optokinetic nystagmus of medium amplitude occurred to the left and was fairly active during optokinetic stimulation. Thirty jerks of optokinetic nystagmus were observed in 180 seconds The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 21 /sec and 40 /sec. No optokinetic after nystagmus was observed. The ENG at the bottom of this figure shows that electric stimulation reduced optokinetic nystagmus 16 jerks of optokinetic nystagmus were recorded in 180 seconds and the velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20 /sec.

Table I. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by weak electric stimulation of the neck muscles of rabbits with binocular vision*

Case	Electric stimulation	Optokinetic nystagmus: Velocity of cylinder rotation 0–20°	21–40°	41–60°	61–80°	81–100°	101–120°	121–140°	141–160°	161–180°	Total nystagmus jerks	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after-nystagmus: 1st type	2nd type	Total nystagmus jerks
No. 3	Before stimulation	2	2	4	2	3	2	1	0	0	16	41–60°	0	0	0
	After stimulation	2	4	3	2	1	0	1	0	0	13	21–40°	0	0	0
No. 4	Before stimulation	1	5	3	7	11	20	19	11	4	81	101–120°	0	0	0
	After stimulation	0	3	5	0	13	16	12	4	1	62	101–120°	0	0	0
No. 5	Before stimulation	0	2	1	1	1	0	1	1	0	5	21–40°	0	0	0
	After stimulation	0	4	3	5	0	0	4	2	1	12	101–120°	0	0	0
No. 6	Before stimulation	2	1	0	0	1	0	1	0	0	5	0–20°	1	0	1
	After stimulation	3	1	4	2	0	0	0	1	0	11	41–60°	0	0	0
No. 7	Before stimulation	1	2	2	2	2	1	1	0	1	12	21–40°	0	0	0
	After stimulation	1	3	4	5	4	2	1	2	1	23	61–80°	0	0	0
No. 8	Before stimulation	1	0	0	0	0	0	0	0	1	1	0–20°	0	0	0
	After stimulation	1	3	2	4	3	1	1	2	0	14	61–80°	0	0	0
No. 9	Before stimulation	1	0	0	0	0	0	1	0	0	1	0–20°	0	0	0
	After stimulation	1	1	2	1	2	0	0	0	1	8	41–60°	0	0	0
No. 10	Before stimulation	2	1	1	1	0	0	0	0	0	3	0–20°	2	0	2
	After stimulation	2	3	3	0	1	0	1	0	0	9	41–60°	0	0	0

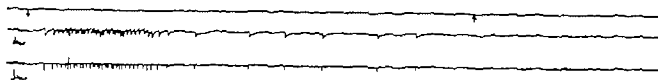
Inverted optokinetic nystagmus

Optokinetic after-nystagmus developed to the right and showed 2 jerks.

Rabbit No. 12: Fig. 4 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the neck muscles of another rabbit with binocular vision. Before electric stimulation, the animal developed inactive optokinetic nystagmus showing 7 jerks of optokinetic nystagmus in 180 seconds and the maximum frequency of nystagmus at a velocity of cylinder rotation of between 0° and 20°/sec. Optokinetic after-nystagmus of medium amplitude occurred to the right and showed one jerk. The ENG at the bottom of this figure shows optokinetic nystagmus and optokinetic after-nystagmus following electric stimulation. The animal developed optokinetic nystagmus of small amplitude to the left when the velocity of cylinder rotation was low but at increased velocity nystagmus to the left disappeared and the inversion phenomenon appeared. Thus, 20 jerks of optokinetic nystagmus were recorded, 11 to the left and 9 to the right (i.e., inverted optokinetic nystagmus). The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20°/sec. Optokinetic after nystagmus developed to the right and showed 13 jerks.

Rabbit No. 13 Fig. 5 shows recordings of optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of another rabbit with binocular vision. Before electric stimulation, the animal developed fairly active optokinetic nystagmus showing 29 jerks in 180 seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 0° and 20°/sec. No optokinetic after nystagmus was observed. After electric stimulation (ENG at bottom of Fig. 5) responses increased markedly to 237 jerks of optokinetic

Before electric stimulation



After strong electric stimulation

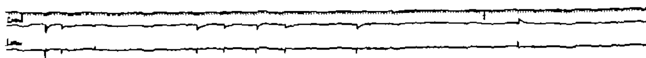
Fig 3 Optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well, although nystagmic responses decreased when the velocity of cylinder rotation increased. After strong electric stimulation, nystagmic responses decreased appreciably in frequency and amplitude, so that the velocity of cylinder rotation giving the maximum frequency of nystagmus decreased. No optokinetic after nystagmus was observed before electric stimulation. However optokinetic after-nystagmus developed to the right and showed two jerks after electric stimulation.

nystagmus in 180 seconds and the maximum frequency of nystagmus at a velocity of cylinder rotation of between 141 /sec and 160 /sec Marked optokinetic after nystagmus also developed to the left showing so called optokinetic nystagmus firing and 94 jerks were recorded

2 *Results in other animals* Table II shows results of strong electric stimulation of the neck muscles in 7 other rabbits Five of these 7 rabbits showed decrease in the total number of nystagmic jerks and 3 of these 5 rabbits also showed the maximum frequency of nystagmus at a decreased velocity of cylinder rotation The sixth rabbit showed no appreciable change in optokinetic nystagmus except that it developed inverted optokinetic nystagmus. The remaining rabbit showed increased optokinetic nystagmus after electric stimulation with increase in the total number of nystagmic jerks and in the velocity of cylinder rotation giving the maximum frequency of nystagmus.

Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by strong electric stimulation

Before electric stimulation



After strong electric stimulation

Fig 4 Optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus was rather inactive. Optokinetic after-nystagmus developed to the right and showed one jerk. After strong electric stimulation, optokinetic nystagmus developed to the left when the velocity of cylinder rotation was low However when the velocity increased, nystagmus to the left disappeared and the inversion phenomenon developed. Optokinetic after-nystagmus to the right appeared and showed 13 jerks.

Before electric stimulation

After strong electric stimulation

Fig. 3. Optokinetic nystagmus and optokinetic after-nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well, although it decreased in frequency when the velocity of cylinder rotation increased. After strong electric stimulation, optokinetic nystagmus increased markedly so that the velocity of cylinder rotation giving the maximum frequency of nystagmus increased. Furthermore, optokinetic after-nystagmus increased greatly. That is, "optokinetic nystagmus firing" developed after strong electric stimulation.

were as follows. 3 of the 7 rabbits showed inhibition of optokinetic nystagmus, but no optokinetic after-nystagmus either before or after *strong electric stimulation. Two other rabbits* showed inhibition of optokinetic nystagmus and increase in optokinetic after nystagmus. The sixth rabbit showed no appreciable change in the total number of optokinetic nystagmus, but showed a marked increase in optokinetic after nystagmus as well as development of inverted optokinetic nystagmus. *The remaining case* showed increased optokinetic nystagmus and inhibited optokinetic after nystagmus. Furthermore, 3 rabbits showed development or increase

Table II. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by strong electric stimulation of the neck muscles of rabbits with binocular vision*

Case	Electric stimulation	Optokinetic nystagmus: 0°–20°	21–40°	41–60°	61–80°	81–100°	101–120°	121–140°	141–160°	161–180°	Total nystagmus jerks	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after nystagmus: 1st type	2nd type	Total nystagmus jerks
No. 14	Before stimulation		5	2	1		3	2	3	2	15	61–100°	0	0	0
	After stimulation	1	1	1	1	1	1		0	0	6	61–80°	0	0	0
No. 15	Before stimulation	0	5	2	2		3	4	4	1	22	81–100°	0	0	0
	After stimulation	0		2	0	0		2	1	1	7	21–40°	0	0	0
No. 16	Before stimulation	4	5		4		1	0	1	0	13	21–40°	0	0	0
	After stimulation	1	5	1	1	1	0	1	0	0	7	21–40°	0	0	0
No. 17	Before stimulation	3	3			1	3	1	5	1	23	41–80°	0	3	3
	After stimulation	3	2	3	2	3	2	1	1	1	17	0–20°	3	7	10
No. 18	Before stimulation	6		3	2	3	0	0	1	1	16	0–20°	0	7	7
	After stimulation	6	5		3	1	1	1		1	23 (2*)	0–20°	0	22	22
No. 19	Before stimulation	8	6	3	3	6 (5*)	2	1		6	27	0–20°	1	3	4
	After stimulation	5	3	1	2	1	1	2	1	5	30	0–20°	14	27	41
No. 20	Before stimulation	2	0	1	1	1	1	0	0	0	6	0–20°	0	0	0
	After stimulation	2	3	2	3	2	1	3	1	0	17	21–40°	0	4	4

* Inverted optokinetic nystagmus

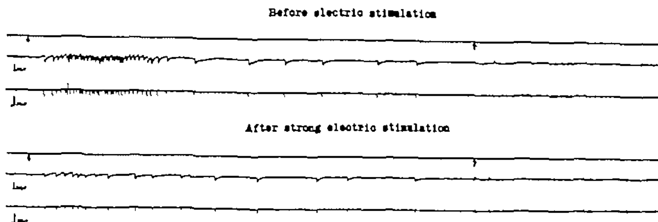


Fig 3 Optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well, although nystagmic responses decreased when the velocity of cylinder rotation increased. After strong electric stimulation, nystagmic responses decreased appreciably in frequency and amplitude, so that the velocity of cylinder rotation giving the maximum frequency of nystagmus decreased. No optokinetic after nystagmus was observed before electric stimulation. However optokinetic after-nystagmus developed to the right and showed two jerks after electric stimulation.

nystagmus in 180 seconds and the maximum frequency of nystagmus at a velocity of cylinder rotation of between 141 /sec and 160°/sec. Marked optokinetic after nystagmus also developed to the left showing so called "optokinetic nystagmus firing" and 94 jerks were recorded.

2. *Results in other animals* Table II shows results of strong electric stimulation of the neck muscles in 7 other rabbits Five of these 7 rabbits showed decrease in the total number of nystagmic jerks and 3 of these 5 rabbits also showed the maximum frequency of nystagmus at a decreased velocity of cylinder rotation. The sixth rabbit showed no appreciable change in optokinetic nystagmus except that it developed inverted optokinetic nystagmus. The remaining rabbit showed increased optokinetic nystagmus after electric stimulation with increase in the total number of nystagmic jerks and in the velocity of cylinder rotation giving the maximum frequency of nystagmus.

Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by strong electric stimulation

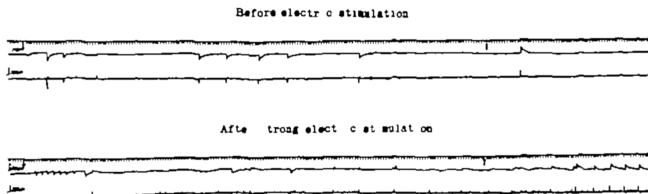


Fig 4 Optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus was rather inactive. Optokinetic after-nystagmus developed to the right and showed one jerk. After strong electric stimulation, optokinetic nystagmus developed to the left when the velocity of cylinder rotation was low However when the velocity increased, nystagmus to the left disappeared and the inversion phenomenon developed. Optokinetic after-nystagmus to the right appeared and showed 13 jerks.

Before electric stimulation

After strong electric stimulation

[illegible]. 5. Optokinetic nystagmus and optokinetic after-nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well, although it decreased in frequency when the velocity of cylinder rotation increased. After strong electric stimulation, optokinetic nystagmus increased markedly so that the velocity of cylinder rotation giving the maximum frequency of nystagmus increased. Furthermore, optokinetic after-nystagmus increased greatly. That is, optokinetic nystagmus "firing" developed after strong electric stimulation.

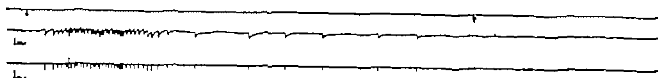
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Table II. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by strong electric stimulation of the neck muscles of rabbits with binocular vision*

Case		Optokinetic nystagmus: 0°–20°	21–40°	41–60°	61–80°	81–100°	101–120°	121–140°	141–160°	161–180°	Total nystagmus stroke	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after-nystagmus: 1st type	2nd type	Total nystagmus stroke
14	Before stimulation	0	2	2	1		3	3	2	2	19	81 100°	0	0	0
	After stimulation	1	1	1	1	1	1	0	0	0	6	0 20°	0	0	0
15	Before stimulation	0	2	2	2	4	3	4		1	22	81 100°	0	0	0
	After stimulation	0		2	0			2	1	1	[illegible]	21 40°	0	0	0
16	Before stimulation	4	5	4			1	0	1	0	23	21– 40°	0	0	0
	After stimulation		2	1	1	1		1	0	0	7	21– 40°	0	0	0
17	Before stimulation	3				2	3	1	2	1	13	41 60°	0	3	3
	After stimulation	3	2	2	2	2	2	1	1	1	17	0– 20°	3	7	10
18	Before stimulation	0		2	2	2	0	0	1	1	10	0– 20°	0	7	7
	After stimulation	0	2	5		1	1	1	1	1	13	0 20°	0	12	12
19	Before stimulation	8	0	3	3	6/2	2	1	1	0	28/2	0– 20°	1	3	4
	After stimulation	5	2		2	1	1	2	1	4	20/5	0– 20°	14	27	41
20	Before stimulation	2	0	1	1	1	1	0	0	0	6	0– 20°	0	5	5
	After stimulation		3	2	3	2	1	3	1	0	17	21– 40°	0	4	4

Inverted optokinetic nystagmus

Before electric stimulation



After strong electric stimulation

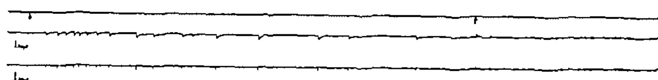


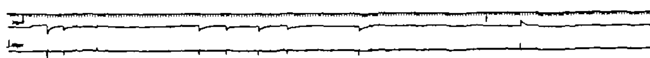
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Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by strong electric stimulation

Before electric stimulation



After strong electric stimulation

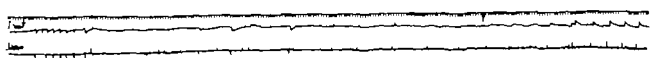
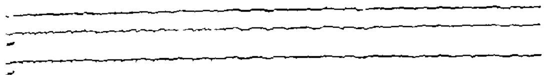
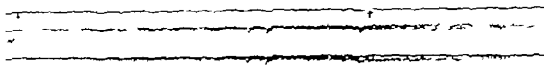


Fig 4 Optokinetic nystagmus and optokinetic after nystagmus before and after strong electric stimulation of the deep nuchal muscles of a rabbit with binocular vision. Before electric stimulation, optokinetic nystagmus was rather inactive. Optokinetic after-nystagmus developed to the right and showed one jerk. After strong electric stimulation, optokinetic nystagmus developed to the left when the velocity of cylinder rotation was low. However when the velocity increased, nystagmus to the left disappeared and the inversion phenomenon developed. Optokinetic after-nystagmus to the right appeared and showed 13 jerks.





ig. 3. Optokinetic nystagmus and optokinetic after-nystagmus before and after strong electric stimulation of he deep nuchal muscles of rabbit with binocular vision. efore electric stimulation, optokinetic nystagmus leveloped fairly well, although it decreased in frequency hen the velocity of cylinder rotation increased. After strong electric stimulation, optokinetic nystagmus increased markedly so that the velocity of cylinder rotation giving the maximum frequency of nystagmus increased. Furthermore, optokinetic after-nystagmus increased greatly. That is, optokinetic nystagmus firing developed after strong electric stimulation.

were as follows. 3 of the 7 rabbits showed inhibition of optokinetic nystagmus, but no optokinetic after-nystagmus either before or after strong electric stimulation. Two other rabbits showed inhibition of optokinetic nystagmus and increase in optokinetic after-nystagmus. The sixth rabbit showed no appreciable change in the total number of optokinetic nystagmus, but showed a marked increase in optokinetic after nystagmus as well as development of inverted optokinetic nystagmus. The remaining case showed increased optokinetic nystagmus and inhibited optokinetic after nystagmus. Further more, 3 rabbits showed development or increase

Table II. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by strong electric stimulation of the neck muscles of rabbits with binocular vision*

Case	Stimulation	Optokinetic nystagmus: 0 20°	21 40°	41 60°	61 80°	81 100°	101 120°	121 140°	141 160°	161 180°	Total nystagmus per/m	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after nystagmus: 1st type	2nd type	Total nystagmus per/m
14	Before stimulation	6	2	2	1		3	3	8	2	19	81 100°	0	0	0
	After stimulation		1	1	1		1	0	0	0	4	61- 30°	0	0	0
15	Before stimulation	6	2	2	2		3		4	1	23	81 100°	0	0	0
	After stimulation	6	1			0	0	2	1	1	[illegible]	21 40°	0	0	0
16	Before stimulation		3				1	0	1	0	10	21- 40°	0	0	0
	After stimulation	1	2	1	1	1	0	1	0	0	7	21 40°	0	0	0
17	Before stimulation	3	3		4	2	3	1	2	1	10	41- 80°	0	3	3
	After stimulation	3	2	3	2	2	2	1	1	1	17	81- 30°	3	7	10
18	Before stimulation	6		2	3	3	0		1	1	18	81- 20°	0	7	7
	After stimulation	0	5	3 1	3	1	1	1		1	[illegible]	81- 20°	0	12	12
19	Before stimulation	3	0	3	3	1	2	2		0	22	0 30°	1	3	
	After stimulation	5	2	1	2		1	2			20	81- 30°	14	37	61
20	Before stimulation	2	0	1	1	1	1	0	0	0	6	81- 20°	0	0	0
	After stimulation	2	3	3	3	2	1	3	1	0	17	21 40°	0	4	

Before electric stimulation



After weak electric stimulation

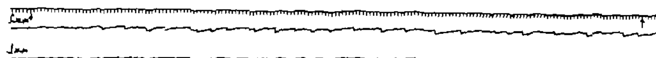


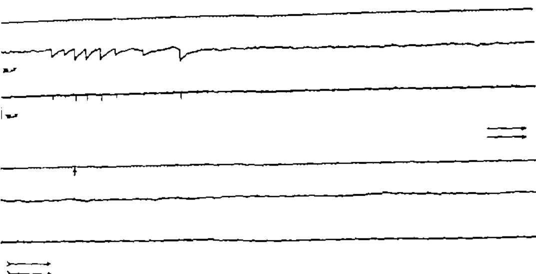
Fig 6 Optokinetic nystagmus and optokinetic after nystagmus before and after weak electric *stimulation* of the deep nuchal muscles of a rabbit with monocular vision. Before electric stimulation, optokinetic nystagmus developed fairly well when the velocity *of cylinder* rotation was low However it became irregular and inactive as the velocity *of* cylinder rotation increased. Optokinetic after-nystagmus developed to the left and showed one jerk. After weak electric stimulation, optokinetic nystagmus became regular and increased in frequency and amplitude. No optokinetic after-nystagmus was observed.

in the inversion phenomenon of optokinetic nystagmus, with or without reduction in the total number of nystagmic jerks of this nystag mus after strong electric stimulation

(II) EXPERIMENT II

1 *Representative cases* Rabbit No 21 Fig. 6 *shows recordings of optokinetic nystagmus and* optokinetic after nystagmus before and after weak electric stimulation of the deep nuchal *muscles of a rabbit with monocular vision.* Before electric stimulation optokinetic nystagmus was fairly regular when the velocity of cylinder *rotation was low* However it became irregular and *inactive* as the velocity *of cylinder rotation* increased A total of 14 jerks of optokinetic nystagmus were recorded in *180* seconds. The velocity of cylinder rotation giving the maximum frequency of nystagmus was between 21 /sec and 40 /sec. Optokinetic *after nystagmus developed* to the left and showed one jerk. The ENG at the *bottom of this figure shows* that after electric stimulation, the animal *developed fairly regular* optokinetic nystagmus in response to an in creased velocity of cylinder rotation and 26 jerks of optokinetic nystagmus were recorded in 180 seconds. The velocity *of cylinder rotation giving* the maximum frequency of nystagmus was between 21 /sec and 40°/sec. No optokinetic after nystagmus was observed

Rabbit No 22 Fig. 7 shows *recordings of* optokinetic nystagmus and *optokinetic* after nystagmus before and after weak electric stimulation of the deep nuchal muscles of a rabbit with monocular vision Before electric stimulation the animal showed inactive optokinetic nystagmus *in response to an optokinetic stimulus mov* ing in the direction from the blindfolded eye to the open eye. No optokinetic nystagmus was *observed when the velocity of cylinder rotation* increased So only 8 jerks of optokinetic nystagmus were recorded in 180 seconds. The velocity *of cylinder rotation giving the maximum frequency of* nystagmus was between 0 and 20°/sec. No optokinetic after nystagmus was observed. *The ENG at the bottom of this figure* shows optokinetic nystagmus and optokinetic after nystagmus following electric stimulation The *animal developed very inactive optokinetic nys*tagmus with a low frequency and amplitude. Furthermore it showed the inversion phenome*non of optokinetic nystagmus* as the velocity of cylinder rotation increased. Thus, 5 jerks of optokinetic nystagmus were recorded, 2 to the left and 3 to the right (i e., *inverted optokinetic nystagmus)* The *velocity of cylinder rotation* giving the maximum frequency of nystagmus was



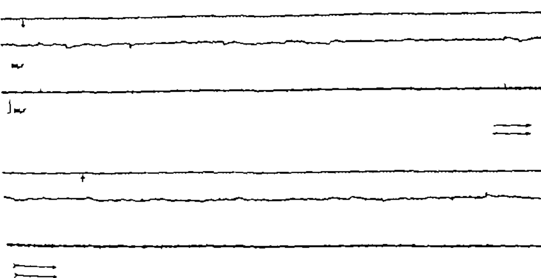


Fig. 7. Optokinetic nystagmus and optokinetic after-nystagmus before and after weak electric stimulation of the deep nuchal muscles of rabbit with monocular vision. Before electric stimulation, optokinetic nystagmus was regular although it disappeared when the velocity of cylinder rotation increased. *No optokinetic after-nystagmus was observed. After weak electric stimulation,* optokinetic nystagmus became very inactive and the inversion phenomenon of optokinetic nystagmus appeared as the velocity of cylinder rotation increased. Optokinetic after-nystagmus to the right and to the left *developed and showed 3 jerks.*

between 0° and 20°/sec. Optokinetic after-nystagmus gave 3 jerks, 2 to the right and 1 to the left.

2. *Results in other animals.* Table III shows results of weak electric stimulation of the neck muscles in 8 other rabbits. Of these 5 rabbits showed an increase in the total number of nystagmic jerks after the stimulation, although

Table III. *Changes in optokinetic nystagmus and optokinetic after-nystagmus caused by weak electric stimulation of the neck muscles of rabbits with monocular vision*

Case	Electric stimulation	Optokinetic nystagmus: Velocity of cylinder rotation 0–20	21–40	41–60	61–80	81–100*	101–120	121–140	141–160	161–180*	Total nystagmic jerks	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after-nystagmus: 1st type	2nd type	Total nystagmic jerks
No. 3	Before stimulation	0	1	2	2	1	2	2	2	2	14	41 ~ 60	0	0	0
	After stimulation	1	3	4	3	4	4	3	3	2	27	41 ~ 60	0	0	0
No. 4	Before stimulation	0	1	2	0	1	0	0	1	0	5	41 ~ 60*	0	1	1
	After stimulation	1	0	0	0	0	0	0	0	0	1	0 ~ 20	0	16	16
No. 5	Before stimulation	1	0	0	1	0	0	1	1	0	4	0 ~ 20	1	0	1
	After stimulation	0	1	4	1 / 1	0	2	1	1	0	3 / 8	21 ~ 40	0	2	2
No. 6	Before stimulation	1	0	0	0	0	0	1	1	0	3	0 ~ 20	0	0	0
	After stimulation	1	3	2	2	1	2	2	2	2	17	21 ~ 40	1	0	1
No. 7	Before stimulation	1	0	1	1	0	0	0	1	0	4	0 ~ 20	0	0	0
	After stimulation	1	4	2	1	1	1	1	1	1	13	21 ~ 40	0	0	0
No. 8	Before stimulation	1	0	0	0	0	0	0	0	0	1	0 ~ 20*	0	0	0
	After stimulation	1	1	1	0	1	1	1	1	0	7	0 ~ 20	0	2	2
No. 9	Before stimulation	0	2	1	0	1	0	0	1	0	5	21 ~ 40	0	1	1
	After stimulation	4	5	1	1	0	1	0	1	0	13	21 ~ 40	0	0	0
No. 10	Before stimulation	3	2	1	0	1	1	0	0	0	8	0 ~ 20	0	0	0
	After stimulation	4	2	2	1 / 2	2 / 2	0	1	1	0	13 / 4	0 ~ 20	3	8	11

* Inverted optokinetic nystagmus

increase in the velocity of cylinder rotation giving the maximum frequency of nystagmus was less obvious. Only one rabbit showed a decrease in the total number of nystagmic jerks and in the velocity of cylinder rotation giving the maximum frequency of nystagmus. The other two showed the inversion phenomenon of optokinetic nystagmus, with and without increase in the total number of nystagmic jerks of this nystagmus.

Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by weak electric stimulation were as follows. Five of the 8 rabbits showed promotion of optokinetic nystagmus, without any appreciable change in optokinetic after nystagmus following electric stimulation. One of the 8 rabbits showed inhibition of optokinetic nystagmus and marked intensification of pre-existing optokinetic after nystagmus. The other two showed inverted optokinetic nystagmus and one of these developed a marked optokinetic after nystagmus.

COMMENT

(1) Correlation between the intensity of electric stimuli given to the deep nuchal muscles and resulting changes in optokinetic eye reflexes

In the present work rabbits with binocular vision tended to show increased optokinetic nystagmus when a weak electric stimulus was given to the neck muscles. In contrast, when a strong stimulus was given, similar rabbits tended to show inhibition of optokinetic nystagmus or in some cases, the inversion phenomenon. These results suggest that there is a close relationship between the optic organ and the cervical proprioceptors in maintenance of body equilibrium and that the cervical proprioceptors can function in two opposing mechanisms which result in either increase or decrease in equilibrium function of the optokinetic system. That is, the mechanism resulting in increased equilibrium function of the optokinetic system seems to be correlated intimately with adequate excita-

tion of the cervical proprioceptors, while the mechanism resulting in decreased function seems to be closely correlated with over-excitement of these receptors. It is of great importance that the proprioceptors, which originally act to promote equilibrium function of the eye and body can produce dysfunction of the optokinetic system if these receptors show over-excitement in response to strong electric stimulation. These characteristics of the proprioceptors are essentially similar to those of the labyrinth, which were originally found by Fukuda and were analyzed under the concept of "two phases of the labyrinthine reflex (Fukuda 1958*a*, *b*).

In short, it is, we feel, valuable to have clarified that Fukuda's concept of the labyrinthine reflex is applicable in interpreting the proprioceptive reflexes from the standpoint of body equilibrium. Furthermore, the fact that strong electric stimulation of the deep nuchal muscles can induce abnormal optokinetic eye reflexes, such as inactive optokinetic nystagmus and inverted optokinetic nystagmus, is helpful in understanding the mechanism of vertigo of cervical origin, since we can often see such abnormal optokinetic eye reflexes in cases with whiplash injury who complained of neck pain and vertigo

(2) Correlation between optokinetic nystagmus and optokinetic after nystagmus in relation to the activity of the cervical proprioceptors, and the origin of optokinetic after-nystagmus

The present work showed that electric stimulation of the deep nuchal muscles of rabbits affected both the development of optokinetic nystagmus and optokinetic after nystagmus, and that promotion of optokinetic after nystagmus tended to be accompanied by inhibition of optokinetic nystagmus or in some cases, by the appearance of inverted optokinetic nystagmus. In contrast, inhibition of optokinetic after nystagmus tended to appear in parallel with promotion of optokinetic nystagmus. Furthermore, the former finding was often observed on strong electric stimulation of the neck muscles, while the latter was observed on weak electric stimulation.

Optokinetic nystagmus is believed to be the ocular equilibrium reflex which maintains a moving object in the fovea, and consequently enables the subject to adapt to rapid changes of the surroundings. However the physiological significance of optokinetic after nystagmus has not been studied from the standpoint of body equilibrium. So it is, we feel, valuable to have clarified that optokinetic after nystagmus differs greatly in behavior from optokinetic nystagmus in relation to the activity of the cervical proprioceptors. From this fact, we can say that first, optokinetic after-nystagmus can be regarded as a sign of dysfunction of the optokinetic system from the standpoint of body equilibrium and second, the cervical proprioceptors, as an organ of equilibrium, can exert two different actions on the optokinetic eye reflexes, i.e., promotion of optokinetic nystagmus and inhibition of optokinetic after-nystagmus.

It is generally believed that marked inhibition of optokinetic nystagmus or inverted optokinetic nystagmus is due to dysfunction of the central nervous system, particularly the brain stem reticular formation. The present examinations revealed that optokinetic after-nystagmus tended to appear or increase in parallel with inhibition of optokinetic nystagmus or in some cases, it was accompanied by the appearance or intensification of inverted optokinetic nystagmus. Furthermore, Hinoki found from studies on the EEG that the strong electric stimulus used in this experiment when applied to the deep nuchal muscles of rabbits can produce dysfunction of the brain stem reticular formation (Hinoki, 1970). From these facts, it seems that optokinetic after-nystagmus, of both the 1st and 2nd types, is of central origin and is especially correlated with dysfunction of the brain stem reticular formation. This consideration is compatible with opinions of many workers since the work of Bárány Naturally the brain stem should not be considered as uniquely responsible for the formation of optokinetic after nystagmus, because Morimoto et al. (1963) found that the cerebrum and the cerebellum are also correlated with the formation of this.

(3) Effects of electric stimulation of the deep

Table III *Changes in optokinetic nystagmus and optokinetic after nystagmus caused by weak electric stimulation of the neck muscles of rabbits with monocular vision*

Case	Electric stimulation	Optokinetic nystagmus: velocity of cylinder rotation 0–20	21–40	41–60	61–80	81–100*	101–120	121–140	141–160*	161–180	Total nystagmic jerks	Velocity of cylinder rotation giving the maximum frequency of nystagmus	Optokinetic after nystagmus: 1st type	2nd type	Total nystagmic jerks
Lt 3	Before stimulation	0	1	2	2	1	2	2	2	2	14	41 – 60	0	0	0
	After stimulation	1	3	4	3	4	4	3	3	2	27	41 – 60	0	0	0
Lt 4	Before stimulation	0	1	2	0	1	0	0	1	0	5	41 – 60	0	1	1
	After stimulation	1	0	0	0	0	0	0	0	0	1	0 – 20*	0	16	16
Lt 5	Before stimulation	1	0	0	1	0	0	1	1	0	4	0 – 20	1	0	1
	After stimulation	0	1	4	1/1	0	2	1	1	0	[illegible]	21 – 40	0	2	2
Lt 6	Before stimulation	1	0	0	0	0	0	1	1	0	3	0 – 20	0	0	0
	After stimulation	1	3	2	2	1	2	2	2	2	17	21 – 40*	1	0	1
Lt 7	Before stimulation	1	0	1	1	0	0	0	1	0	4	0 – 20	0	0	0
	After stimulation	1	4	2	1	1	1	1	1	1	13	21 – 40	0	0	0
Lt 8	Before stimulation	1	0	0	0	0	0	0	0	0	1	0 – 20	0	0	0
	After stimulation	1	1	1	0	1	1	1	1	0	7	0 – 20	0	2	2
Lt 9	Before stimulation	0	2	1	0	1	0	0	1	0	5	21 – 40	0	1	1
	After stimulation	4	5	1	1	0	1	0	1	0	13	21 – 40*	0	0	0
Lt 10	Before stimulation	3	2	1	0	1	1	0	0	0	8	0 – 20	0	0	0
	After stimulation	4	2	2	1/3	3/2	0	1	1	0	13/[illegible]	0 – 20	3	8	11

* Inverted optokinetic nystagmus

increase in the velocity of cylinder rotation giving the maximum frequency of nystagmus was less obvious. Only one rabbit showed a decrease in the total number of nystagmic jerks and in the velocity of cylinder rotation giving the maximum frequency of nystagmus. The other two showed the inversion phenomenon of optokinetic nystagmus, with and without increase in the total number of nystagmic jerks of this nystagmus.

Results on changes in the relationship between optokinetic nystagmus and optokinetic after nystagmus caused by weak electric stimulation were as follows. Five of the 8 rabbits showed promotion of optokinetic nystagmus, without any appreciable change in optokinetic after nystagmus following electric stimulation. One of the 8 rabbits showed inhibition of optokinetic nystagmus and marked intensification of pre-existing optokinetic after nystagmus. The other two showed inverted optokinetic nystagmus and one of these developed a marked optokinetic after nystagmus.

COMMENT

(1) Correlation between the intensity of electric stimuli given to the deep nuchal muscles and resulting changes in optokinetic eye reflexes

In the present work rabbits with binocular vision tended to show increased optokinetic nystagmus when a weak electric stimulus was given to the neck muscles. In contrast when a strong stimulus was given, similar rabbits tended to show inhibition of optokinetic nystagmus or in some cases, the inversion phenomenon. These results suggest that there is a close relationship between the optic organ and the cervical proprioceptors in maintenance of body equilibrium and that the cervical proprioceptors can function in two opposing mechanisms which result in either increase or decrease in equilibrium function of the optokinetic system. That is the mechanism resulting in increased equilibrium function of the optokinetic system seems to be correlated intimately with adequate excita

Table IV Changes in correlations between inverted optokinetic nystagmus, optokinetic nystagmus and optokinetic after-nystagmus caused by electric stimulation of the neck muscles of rabbits

[illegible]		Inverted optokinetic nystagmus			Optokinetic nystagmus			Optokinetic after-nystagmus		
		Appearance or Increase	No significant change	Disappearance or Decrease	Increase	No significant change	Decrease	Appearance or Increase	No significant change	Disappearance or Decrease
Binocular vision	1V 90	0	0	3	3	0	0	0	2	0
	15V 90	4	0	0	0	2	2	3	1	0
Monocular vision	1V 90	3	0	0	1	1	1	2	1	0

the appearance or intensification of optokinetic after-nystagmus.

(2) The appearance or intensification of this phenomenon tended to develop in parallel with inhibition of optokinetic nystagmus. It was also fairly well correlated with development or intensification of optokinetic after-nystagmus.

(3) When weak electric stimulation was given to the deep nuchal muscles of rabbits with binocular vision, the animals showed the phenomena described in (1). In contrast, when strong electric stimulation was given to the same muscles, the animals tended to show the phenomena described in (2). On weak electric stimulation of the same muscles of rabbits with monocular vision, some rabbits developed inverted optokinetic nystagmus, which was fairly well correlated with the appearance or intensification of optokinetic after-nystagmus. However a less clear correlation was found between inverted optokinetic nystagmus and optokinetic nystagmus in these animals.

Hinoki, one of the present authors, found that after weak electric stimulation of the neck muscles, many rabbits with binocular vision showed an arousal reaction in the EEG in response to optokinetic stimulation, whereas after strong electric stimulation, similar rabbits tended to show a sluggish arousal reaction in the EEG (Hinoki, 1972).

Rabbits with monocular vision also tended to show activation of the EEG in response to optokinetic stimulation after weak electric stimulation of the neck muscles. However the arousal reaction in the EEG was less obvious in these animals. Furthermore, a few of these animals showed reduction in the arousal reaction (Hinoki et al., to be published).

These results suggest that the inversion phenomenon of optokinetic nystagmus seen in the present experiments is due to dysfunction of the brain stem reticular formation, which is mainly induced by over-excitement of the cervical proprioceptors.

Morimoto and his co-workers found that when accelerative optokinetic stimulation was given repeatedly at short intervals, several rabbits developed eye movements resembling "nystagmus clonus" or "firing" in which nystagmus occurred very actively and independently of the original optokinetic stimuli and lasted for a long time after cessation of optokinetic stimulation (Morimoto et al., 1963). They also found that this phenomenon was more easily elicited after removal of the brain cortex of rabbits (Morimoto et al., 1963). In our experiments, this phenomenon was never observed in rabbits with inactive optokinetic nystagmus before electric stimulation of the neck muscles. Furthermore, it only developed on strong electric stimulation. Bender

nuchal muscles on the unidirectional responsiveness of the eye to optokinetic stimulation in rabbits with one eye

Fukuda & Tokita found that animals with completely crossed optic nerves, such as fowls and rabbits, develop very inactive optokinetic eye and body reflexes when they are given optokinetic stimuli moving from the side of the blindfolded eye to that of the open eye. Of course, they can respond appreciably to an optokinetic stimulus in the opposite direction. Fukuda named this phenomenon the unidirectionality of the optokinetic reflex (Fukuda & Tokita, 1957). This unidirectional responsiveness of the eye to optokinetic stimulation can be significantly improved by simultaneous application of a weak labyrinthine stimulation and the animals then respond fairly well to optokinetic stimuli to which the optic organ alone cannot react (Fukuda, 1959)

The question then arises of whether the cervical proprioceptors can exert a similar function to that of the labyrinth just mentioned The present examinations revealed that after weak electric stimulation of the deep nuchal muscles, about half of the rabbits with monocular vision *responded fairly well to an optokinetic stimulus* moving from the side of the blindfolded eye to that of the open eye and consequently showed promotion of optokinetic nystagmus. This means that the cervical proprioceptors can participate in the compensatory mechanism of the unidirectional responsiveness of the eye to optokinetic stimulation in rabbits with one eye However this compensatory mechanism of the cervical proprioceptors is not effective enough to allow rabbits with monocular vision to respond well to an optokinetic stimulus moving from the side of the blindfolded eye to that of the open eye For example, promotion of optokinetic nystagmus caused by weak electric stimulation was less obvious in these animals. Furthermore some of these animals showed inverted optokinetic nystagmus as well as activation of optokinetic after nystagmus. Naturally in the daily life of rabbits with one eye not only the cervical proprioceptors but also the labyrinth can participate in the compensatory mechanism of the unidirectional responsiveness of the eye to optokinetic stimulation at times such as during active rotation. Thus, animals with one eye can respond well to an optokinetic stimulus moving from the blindfolded eye to that of the open eye. This assumption is supported by the fact that after weak electric stimulation of the deep nuchal muscles, many rabbits with one eye show active perrotatory eye nystagmus in response to a rotatory stimulus produced by subliminal rotation from the side of the open eye to that of the blindfolded eye (Koike, 1971). Of course, during such rotation, rabbits with one eye receive an optokinetic stimulus from the side of the blindfolded eye to that of the open eye, which is induced by relative movements of the external world due to chair rotation.

(4) The inversion phenomenon of optokinetic nystagmus and so called "optokinetic nystagmus firing in relation to the activity of the cervical proprioceptors

The inversion phenomenon of optokinetic nystagmus is sometimes observed in patients with lesions of the brain stem such as brain tumor head trauma and circulatory disorders of this part of the brain The following observations have been made on the relationship between this phenomenon and the activity of the cervical proprioceptors. Ushio one of our coworkers, found that the inversion phenomenon of optokinetic nystagmus was observed in vertigo cases with whiplash injury and that this phenomenon seemed to have a positive correlation with hypertonicity of the cervical erector muscles (Ushio et al., 1971) However no systematic and experimental studies have been made from this point of view Table IV shows changes in the correlation between optokinetic nystagmus, optokinetic after nystagmus and inverted optokinetic nystagmus caused by electric stimulation of the neck muscles. From this table the following conclusions are drawn

(1) Disappearance of inverted optokinetic nystagmus was parallel with promotion of optokinetic nystagmus. Furthermore disappearance of this phenomenon was i

Table IV *Changes in correlations between inverted optokinetic nystagmus, optokinetic nystagmus and optokinetic after-nystagmus caused by electric stimulation of the neck muscles of rabbits*

[illegible]		Inverted optokinetic nystagmus			Optokinetic nystagmus			Optokinetic after-nystagmus		
		Appearance or Increase	No significant change	Disappearance or Decrease	Increase	No significant change	Decrease	Appearance or Increase	No significant change	Disappearance or Decrease
Binocular vision	1V; 90	0	0	3	3	0	0	0	3	0
	15V; 90	4	0	0	0	2	2	3	1	0
Monocular vision	1V 90	3	0	0	1	1	1	2	1	0

the appearance or intensification of optokinetic after-nystagmus.

(2) The appearance or intensification of this phenomenon tended to develop in parallel with inhibition of optokinetic nystagmus. It was also fairly well correlated with development or intensification of optokinetic after nystagmus.

(3) When weak electric stimulation was given to the deep nuchal muscles of rabbits with binocular vision, the animals showed the phenomena described in (1). In contrast, when strong electric stimulation was given to the same muscles, the animals tended to show the phenomena described in (2). On weak electric stimulation of the same muscles of rabbits with monocular vision, some rabbits developed inverted optokinetic nystagmus, which was fairly well correlated with the appearance or intensification of optokinetic after-nystagmus. However a less clear correlation was found between inverted optokinetic nystagmus and optokinetic nystagmus in these animals.

Ishida, one of the present authors, found that after weak electric stimulation of the neck muscles, many rabbits with binocular vision showed an arousal reaction in the EEG in response to optokinetic stimulation, whereas after strong electric stimulation, similar rabbits tended to show a sluggish arousal reaction in the EEG (Ishida, 1972).

Rabbits with monocular vision also tended to show activation of the EEG in response to optokinetic stimulation after weak electric stimulation of the neck muscles. However the arousal reaction in the EEG was less obvious in these animals. Furthermore, a few of these animals showed reduction in the arousal reaction (Hinoki et al., to be published).

These results suggest that the inversion phenomenon of optokinetic nystagmus seen in the present experiments is due to dysfunction of the brain stem reticular formation, which is mainly induced by over-excitement of the cervical proprioceptors.

Morimoto and his co-workers found that when accelerative optokinetic stimulation was given repeatedly at short intervals, several rabbits developed eye movements resembling "nystagmus clonus" or "firing" in which nystagmus occurred very actively and independently of the original optokinetic stimuli and lasted for a long time after cessation of optokinetic stimulation (Morimoto et al., 1963). They also found that this phenomenon was more easily elicited after removal of the brain cortex of rabbits (Morimoto et al., 1963). In our experiments, this phenomenon was never observed in rabbits with inactive optokinetic nystagmus before electric stimulation of the neck muscles. Furthermore, it only developed on strong electric stimulation. Bender

nuchal muscles on the unidirectional responsiveness of the eye to optokinetic stimulation in rabbits with one eye

Fukuda & Tokita found that animals with completely crossed optic nerves such as fowls and rabbits, develop very inactive optokinetic eye and body reflexes when they are given optokinetic stimuli moving from the side of the blindfolded eye to that of the open eye. Of course, they can respond appreciably to an optokinetic stimulus in the opposite direction Fukuda named this phenomenon "the unidirectionality of the optokinetic reflex" (Fukuda & Tokita, 1957). This unidirectional responsiveness of the eye to optokinetic stimulation can be significantly improved by simultaneous application of a weak labyrinthine stimulation and the animals then respond fairly well to optokinetic stimuli to which the optic organ alone cannot react (Fukuda, 1959).

The question then arises of whether the cervical proprioceptors can exert a similar function to that of the labyrinth just mentioned The present examinations revealed that after weak electric stimulation of the deep nuchal muscles, about half of the rabbits with monocular vision responded fairly well to an optokinetic stimulus moving from the side of the blindfolded eye to that of the open eye and consequently showed promotion of optokinetic nystagmus. This means that the cervical proprioceptors can participate in the compensatory mechanism of the unidirectional responsiveness of the eye to optokinetic stimulation in rabbits with one eye. However this compensatory mechanism of the cervical proprioceptors is not effective enough to allow rabbits with monocular vision to respond well to an optokinetic stimulus moving from the side of the blindfolded eye to that of the open eye For example, promotion of optokinetic nystagmus caused by weak electric stimulation was less obvious in these animals. Furthermore, some of these animals showed inverted optokinetic nystagmus as well as activation of optokinetic after nystagmus. Naturally in the daily life of rabbits with one eye not only the cervical proprioceptors but also the labyrinth can participate in the compensatory mechanism of the unidirectional responsiveness of the eye to optokinetic stimulation at times such as during active rotation. Thus, animals with one eye can respond well to an optokinetic stimulus moving from the blindfolded eye to that of the open eye. This assumption is supported by the fact that after weak electric stimulation of the deep nuchal muscles, many rabbits with one eye show active perrotatory eye nystagmus in response to a rotatory stimulus produced by subliminal rotation from the side of the open eye to that of the blindfolded eye (Koike, 1971). Of course, during such rotation, rabbits with one eye receive an optokinetic stimulus from the side of the blindfolded eye to that of the open eye, which is induced by relative movements of the external world due to chair rotation

(4) The inversion phenomenon of optokinetic nystagmus and so called "optokinetic nystagmus firing in relation to the activity of the cervical proprioceptors

The inversion phenomenon of optokinetic nystagmus is sometimes observed in patients with lesions of the brain stem such as brain tumor head trauma and circulatory disorders of this part of the brain. The following observations have been made on the relationship between this phenomenon and the activity of the cervical proprioceptors. Ushio one of our coworkers, found that the inversion phenomenon of optokinetic nystagmus was observed in vertigo cases with whiplash injury and that this phenomenon seemed to have a positive correlation with hypertonicity of the cervical erector muscles (Ushio et al. 1971) However no systematic and experimental studies have been made from this point of view Table IV shows changes in the correlation between optokinetic nystagmus optokinetic after nystagmus and inverted optokinetic nystagmus caused by electric stimulation of the neck muscles From this table the following conclusions are drawn

(1) Disappearance of inverted optokinetic nystagmus was parallel with promotion of optokinetic nystagmus. Furthermore, disappearance of this phenomenon was not accompanied by

formation. Furthermore, this tract changes neurons in these parts of the brain and terminates in the superior colliculus (Nauta & Kuypers, 1958). In addition, this tract sends some fibers to Deiters nucleus (Terada, 1960; Niimi et al., 1960).

On the other hand, neural elements connecting the cervical proprioceptors to the cerebellum involve the cuneocerebellar tract and the spino-olivo-cerebellar tract, especially the former.

In short, impulses from the optic organ and the cervical proprioceptors may be integrated mainly in the brain stem reticular formation, with or without direct collaboration with the cerebellum and the vestibular nuclei. Of course, this idea is based on observations on rabbits. In man and animals, such as monkeys, neural elements of higher order, particularly the brain cortex should be taken into consideration in assessing the mechanism of optic proprioceptive coordination. Furthermore, the following mechanism seems important in speculating on this problem. Tokita et al. reported that nystagmogenic areas in the meso-diencephalon, originally found by Lachmann and his co-workers, are important in the formation of optic vestibular coordination (Lachmann et al., 1958, Tokita et al., 1964). These areas seem correlated with production of optic proprioceptive coordination, since the midbrain reticular formation, which is important in eliciting central nystagmus, connects with the cervical proprioceptors through the spinoreticular tract.

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ZUSAMMENFASSUNG

Zwei Versuche über die funktionelle Korrelation zwischen dem Sehorgan und den zervikalen Propriozeptoren in der Erhaltung des Körpergleichgewichts wurden durchgeführt.

Versuch I. Die Auswirkungen schwacher und starker elektrischer Stimulation der tiefen Nackenmuskeln auf die Veränderungen des optokinetischen Nystagmus und des optokinetischen Nachnystagmus wurden bei erwachsenen Non-albino-Kaninchen mit Binokularsehen überprüft.

Versuch II. Versuch I wurde bei Kaninchen mit Monokularsehen wiederholt, wobei ein optokinetischer Reiz von der Seite des verbundenen Auges aus auf die Seite des offenen Auges und nur ein schwacher elektrischer Reiz auf die Nackenmuskeln ausgeübt wurden.

Folgende Resultate wurden erzielt.

1) Versuch I. Schwache elektrische Stimulation der tiefen Nackenmuskeln von Kaninchen mit Binokularsehen zeigte die Tendenz, einen optokinetischen Nystagmus zu fördern, wobei sich entweder keine deutliche Veränderung oder eine Abnahme des optokinetischen Nachnystagmus zeigte. Starke elektrische Stimulation hatte entgegengesetzte Auswirkungen, d. h., dass sich hierbei die Tendenz zeigte, einen optokinetischen Nystagmus zu hemmen und einen optokinetischen Nachnystagmus zu aktivieren. Starke elektrische Stimulation rief ebenfalls einen anomalen optokinetischen Nystagmus hervor, wie z. B. die Inversion des optokinetischen Nystagmus und „die Faserung des optokinetischen Nystagmus".

2) Versuch II. Schwache elektrische Stimulation der tiefen Nackenmuskeln von Kaninchen mit Monokularsehen hatte ähnliche Auswirkungen wie beim Versuch I. Jedoch war die Förderung des optokinetischen Nystagmus weniger deutlich, während die Aktivierung des optokinetischen Nachnystagmus stärker ausgeprägt war. Ausserdem entwickelte sich die Inversion des optokinetischen Nystagmus sogar bei schwacher elektrischer Stimulation.

Aus diesen Ergebnissen wurden folgende Schlüsse gezogen:

1) Die zervikalen Propriozeptoren können zwei Mechanismen auslösen: Sie können die Gleichgewichtsfunktion des optokinetischen Systems entweder unterstützen oder ausschalten.

2) Die zervikalen Propriozeptoren als Gleichgewichtsorgan können sich in zweifacher Weise auf den optokinetischen Augenreflex auswirken, d. h., sie können den optokinetischen Nystagmus fördern und den optokinetischen Nachnystagmus hemmen.

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studied optokinetic after nystagmus in monkeys and found that once rythmical eye movements, such as optokinetic nystagmus, are set up, they continue of their own accord and become relatively independent of the optokinetic stimuli with regard to their frequency and duration (Bender 1956) His finding is suggestive in speculating on the mechanism of "optokinetic nystagmus firing In any case, the present result is, we feel, valuable because this phenomenon has not been studied in connection with the activity of the cervical proprioceptors.

(5) Mechanism of optic proprioceptive coordination in rabbits from the standpoint of fiber connections of the central nervous system

From our experiments, it seems that the brain stem reticular formation is the most important in the mechanism of integration of impulses from the optic organ and the cervical proprioceptors. We would like here to discuss whether this idea is justifiable from the neuro-anatomical point of view

Recently Fukuda proposed a scheme concerning the optokinetic reflex arc (Fukuda 1967). According to his scheme neural pathways related to the optokinetic eye reflexes involve the following elements, arranged in the following way the retina→the optic nerves→the superior colliculus→the tectocerebellar tract→the cerebellar cortex→the cerebellar nuclei particularly the fastigal nucleus→the vestibular nuclei→the MLF→the oculomotor nuclei→the oculomotor nerves→the eye muscles. Morimoto stressed the importance of the vestibular nuclei in the formation of optokinetic nystagmus, since he found that optokinetic nystagmus could not be induced in a rabbit with bilaterally damaged vestibular nuclei although this nystagmus could be induced slightly about a week after the operation (Morimoto 1955) However there is an uncertain point in Fukuda's scheme because Tashiro studying fiber connections between the superior colliculus and the cerebellum in cats, stated that there were no definite connections between these two parts of the brain (Tashiro 1940) Niimi suggested the possibility of connections between the superior colliculus and the vestibular nuclei through the pontine nucleus, the cerebellar cortex and the cerebellar nucleus (Niimi, 1970) But there is still controversy over his suggestion since the cerebellar nucleus involved in this reflex arc belongs to one developed at a late stage of phylogenesis, while the vestibular nuclei belong to one developed at an earlier stage and it is generally accepted that fiber connections in the central nervous system are formed between neural elements developed at the same stage of phylogenesis.

The other possible neural pathways may involve the following elements, arranged in the following way the retina→the optic nerves→the superior colliculus→tectoreticular fibers→the brain stem reticular formation→the MLF→the oculomotor nuclei→the oculomotor nerves→the eye muscles. Rasmussen found the presence of crossed nerve fibers connecting the superior colliculus to the brain stem reticular formation (Rasmussen, 1936). Tashiro also found that there are two types of tectoreticular fibers, i e. crossed and uncrossed (Tashiro, 1939) Pearce demonstrated that the terminal region of the tectoreticular fibers from the superior colliculus is in the medial part of the pontine and medullary reticular formation including the nuclei reticularis gigantocellularis, pontis caudalis and oralis. While these connections are mainly contralateral, fibers to the midbrain reticular formation are chiefly homolateral (Pearce, 1956).

These findings suggest that optokinetic nystagmus may be mainly formed in the brain stem reticular formation and the superior colliculus independently of the cerebellum and the vestibular nuclei

The spinoreticular tract seems the most important tract connecting the cervical proprioceptors with the central nervous system and particularly the brain stem reticular formation, because this tract originates abundantly in the cervical cord and ascends along the lateral fascicle and the anterior column and terminates in the reticular formation both of the pons and the medulla oblongata (Brodal 1957 Nauta & Kuypers, 1958 Bowsher 1965). Some fibers of this tract ascend directly to the midbrain reticular

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NEUROTOLOGICAL STUDIES ON THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE FORMATION OF TRAUMATIC VERTIGO OF CERVICAL ORIGIN

Manabu Hinoki and Hiroshi Niki

From the Department of Otolaryngology, School of Medicine, Tokushima University, Tokushima, Japan

Abstract. To test the validity of the hypothesis that irritation of the cervical sympathetic nerves is a cause of hypertonicity of the cervical soft supporting tissues, especially the deep nuchal muscles, and that this hypertonicity is a cause of traumatic vertigo of cervical origin, we examined 44 vertigo cases with whiplash injury by testing equilibrium function and EMG discharges from the neck before and after administration of drugs affecting the sympathetic receptors. The results obtained were as follows.

1. Administration of iso-proterenol (beta-receptor stimulant) caused a significant increase in the EMG's from the injured neck muscles, in parallel with increased impairment of the righting reflex. The blindfolded vertical writing test showed the appearance or intensification of ataxia or deviation in writing when this drug was given. In contrast, administration of propranolol (beta-receptor depressor) had the opposite effects on the EMG's, the righting reflex and blindfolded vertical writing. Furthermore, the resulting changes in the EMG's and equilibrium functions were parallel with alterations in subjects' complaints, i.e., increase or decrease in neck pain and vertigo.

2. Administration of drugs affecting the alpha receptors, such as noradrenaline (alpha-receptor stimulant) and phentolamine (alpha-receptor depressor) had no appreciable effect on the EMG's, equilibrium function or the subjects' complaints.

These results show that in vertigo due to whiplash injury hypertonicity of the cervical erector muscles can be induced sympathetically and that this hypertonicity is based on over-excitement of beta receptors in the injured neck muscles, which results in vertigo of cervical origin.

Since the work of Barré it has been widely believed that irritation of the cervical sympathetic nerve is a main cause of vertigo of cervical origin. According to this theory irritation of the cervical sympathetic nerve may result in circulatory disorders either of the vertebral artery or of the internal auditory artery and these disorders are major factors in producing vertigo of cervical origin (Barré, 1926; Lieou, 1928; Maspetiol, 1960). This theory is supported clinically and experimentally and we have taken it into consideration in assessing the mechanism of traumatic vertigo of cervical origin, such as whiplash injury. However, we feel that the importance of the sympathetic nervous system in producing vertigo due to whiplash injury is also related to its effect in producing hypertonicity of the cervical soft supporting tissues and especially the erector muscles of this region for the following reasons. Many traumatic cases with Barré's syndrome which we have examined showed both cervical pain, suggesting hypertonicity of the cervical soft supporting tissues, and abnormal responses of the autonomic nervous system. Furthermore, improvement or aggravation of autonomic nervous syndromes during treatment was parallel with changes in the extent of nuchal pain. For example, among 17 of our clinical cases in which pain in the neck decreased or disappeared during the observation period, 13 cases (76.4%) showed improvement of autonomic syndromes, whereas all the 9 cases in which pain in the neck increased showed aggravation of autonomic syndromes. We also found a close correlation between vertigo and neck pain in cases with whiplash injury. For instance, among 17 of our vertigo cases in which pain in the neck disappeared or decreased during the observation period, 13 cases (76.4%) showed reduction of vertigo. Whereas all the 9 cases in which pain in the neck increased showed aggravation of

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tion of each of these drugs. Then, we observed the relationship between the resulting changes in equilibrium function and those in the EMG's from the neck.

2. Subjects examined

Forty-four cases with whiplash injury aged 15 to 50 were examined by the equilibrium tests mentioned above. The period between the time of the accident and the time of examination varied from as little as one month to as much as 3 years. All cases in which the head had struck a solid object were omitted. So the cases tested had no serious brain symptoms.

3. Results on vertigo cases with whiplash injury using iso-proterenol

(i) *Representative case.* A 31 year-old woman who had sustained whiplash injury 8 months before. After her accident this woman developed swaying of the body associated with pain of the right side of the neck and headache. X Rays of the neck showed no abnormal findings except a slight incongruence of c_3 of the cervical vertebrae. Fig. 1 shows registrograms of movements of the head (bottom) and the EMG's from the neck (upper two rows). After intramuscular injection of iso-proterenol this woman complained that pain in the neck and swaying of the body became much worse. Fig. 1 shows that this was endorsed by a significant increase in abnormal EMG discharges from the neck and swaying of the body (head). It is worth noting that the EMG's from the right of the neck were more abnormal *than those from the left before the* injection, and that after the injection the EMG's from the right of the neck became even more abnormal *with burst-like* muscular discharges.

Fig. 2 shows the blindfolded vertical writing tests of the same subject before and after injection of iso-proterenol. Ten minutes after the injection, her writing became markedly ataxic. This supports the subject's complaint of increased vertigo.

(ii) Results on 13 cases with whiplash injury. In 8 of the 13 cases with whiplash injury tested,

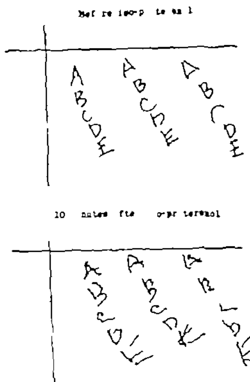


Fig. 2. The blindfolded vertical writing tests of 31-year-old woman with whiplash injury before and after administration of iso-proterenol. After administration of this drug, writing became markedly ataxic. This supported the subject's complaints of increased vertigo.

abnormal EMG's from the neck and disturbances of the righting reflex apparently increased when iso-proterenol was given. Two cases did not show any significant increase in the EMG's, but showed slight aggravation of the righting reflex. In the other 3 neither increase in the EMG's nor in disturbances of the righting reflex was seen.

In the same group 8 cases showed the appearance or intensification of ataxia (particularly tremor-like movements) in the blindfolded vertical writing test. Two cases did not show any ataxia, but showed a significant increase in deviation in writing. In the other 3 no significant changes were observed.

The changes evoked in these cases by drug injection were closely related with complaints of increase in symptoms, such as nuchal pain and vertigo.

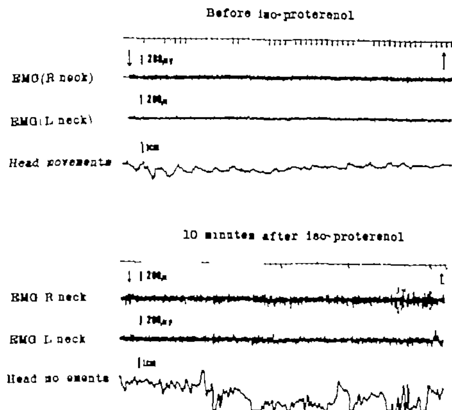


Fig 1 EMG s from the neck and registrograms of movements of the head of a 31 year-old woman with whiplash injury in the position for Mann's test, before and after administration of iso-proterenol. When the drug was injected intramuscularly this subject complained of increased pain in the neck and unsteadiness. This was endorsed by significant increase in abnormal EMG discharges from the neck and swaying of the body (head).

vertigo These results suggest that irritation of the cervical sympathetic nerves can induce hypertonicity of the erector muscles of this region This hypertonicity may also be an etiological factor in causing vertigo due to whiplash injury

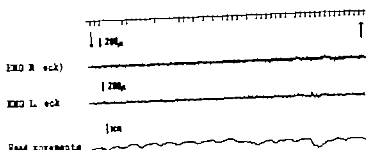
The present work was undertaken to clarify the validity of this idea.

EXPERIMENTAL

1 *Equilibrium tests after treatment with drugs affecting the sympathetic receptors*

Principle and method To test the validity of the hypothesis that irritation of the sympathetic nervous system is a cause of hypertonicity of the cervical soft supporting tissues, which results in vertigo of cervical origin it is necessary to see whether changes in the activity of the sympathetic nervous system can cause decrease or increase in the tonus of the cervical soft supporting tissues and especially the erector muscles of this region and whether the changes in the tonus of the cervical soft supporting tissues thus evoked are parallel with those of vertigo One method used for examining the validity of this assumption is to inject drugs affecting the sympathetic nervous system and then to study the correlation between the consequent changes in the EMG s from the neck region and those in eye and body equilibrium

Ahlquist and other workers found that there are two kinds of sympathetic receptors alpha and beta. Recent investigations revealed that various drugs can stimulate or suppress the activity of either the alpha or beta receptors (Ahlquist 1948). For instance, noradrenaline is known to stimulate the activity of alpha receptors, while phentolamine has the opposite effect on these receptors. Iso-proterenol and propranolol are known to stimulate and depress beta receptors, respectively Thus, we tested the effects of these drugs on the symptoms of vertigo cases with whiplash injury We measured changes in vertigo by examining body equilibrium in various ways, such as by testing the righting reflex (Mann s position) and the arm drift reaction (the blindfolded vertical writing test). We also took EMG records from the neck of the subjects before and 10 minutes after adminis-



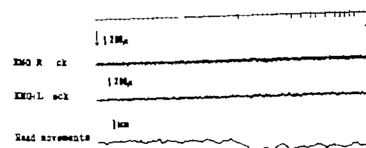


Fig. 5 EMG's from the neck and registrograms of movements of the head of 36-year-old woman with whiplash injury in the position for Mann's test, before and after administration of noradrenaline. After intramuscular injection of noradrenaline this woman reported no significant change in the pain in her neck or her sensation of swaying. This was endorsed by the lack of change in either the EMG's from the neck or registrograms of movements of the head after injection of noradrenaline.

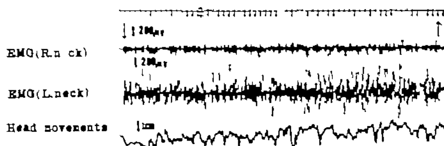
In 10 of the 16 cases with whiplash injury tested, abnormal EMG's from the neck and disturbances of the righting reflex decreased when propranolol was given. One case showed no significant decrease in the EMG's, but improvement of the righting reflex. The other 5 showed neither decrease in the abnormal EMG's nor change in disturbances of the righting reflex.

In the same group, 6 cases, who showed ataxia and deviation in writing showed reduction in these abnormalities after this drug was given. Among 10 cases who showed only deviation in writing, 5 cases showed reduced deviation and 4 cases showed no significant change after injecting the drug. The remaining case developed slight ataxia in writing.

i. Results on vertigo cases with whiplash injury using noradrenaline

(i) Representative case. A 36-year-old woman who sustained whiplash injury when her car was bumped from the rear 6 months previous to examination. She was slightly dazed for about 5 minutes after the accident, but has had no memory defect since that time. She complained of pain of the right side of the neck, headache and a sensation of falling associated with the weather. X Rays of the neck showed no structural abnormality. We tested the effects of noradrenaline on this subject, and observed the resulting changes in the EMG's from the neck and in the righting reflex. Fig. 5 shows the EMG's from the neck and registrograms of movements of the head before and after injection of noradrenaline. There were no demonstrable changes either in the EMG's or in the righting reflex after injecting the drug. The blindfolded vertical writing tests of this subject in Fig. 6 show no apparent change in writing after noradrenaline was given. Furthermore, when we injected noradrenaline into this woman intramuscularly her complaints did not change. This was compatible with the results of the EMG's and the equilibrium tests mentioned above.

(ii) Results on 8 cases with whiplash injury:



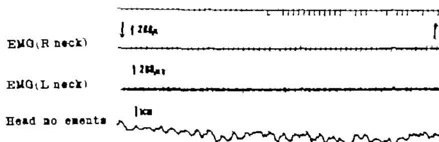
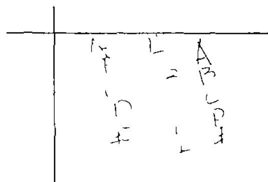


Fig 3. EMGs from the neck and registrograms of movements of the head of a 40-year-old man with whiplash injury in the position for Mann's test, before and after administration of propranolol. After intravenous injection of this drug the subject reported decreased pain in the neck and less sensation of falling. This was endorsed by marked reduction in abnormal EMGs from the neck and in swaying of the body (lower records).



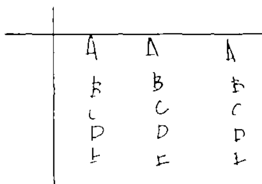


Fig 4 The blindfolded vertical writing tests of a 40-year old man with whiplash injury before and after administration of propranolol. After propranolol deviation in writing almost disappeared and ataxic writing became less. This was parallel with reduction in a sensation of falling.

4 *Results on vertigo cases with whiplash injury using propranolol*

(i) Representative case A 40-year-old man who sustained whiplash injury when his car was bumped by a vehicle 3 months previous to examination. He wad dazed for about 10 minutes after the accident and after one hour he developed pain of the left side of the neck, photophobia and a sensation of falling associated with black-out on standing up X Rays of the cervical spine revealed a slight incongruence ($c_{3,4}$) and loss of the normal cervical curve The nuchal pain and sensation of falling decreased when propranolol was given. This was endorsed by the results shown in Fig. 3 the abnormal EMG discharges from the neck decreased and swaying of the body (head) became much less. Furthermore, this drug effectively reduced the abnormality in muscular discharges from the left of the neck seen before the injection.

Fig. 4 shows the blindfolded vertical writing tests of the same subject before and after injection of propranolol. Deviation in writing almost disappeared and ataxic writing became significantly less. This also indicates decrease in vertigo

(ii) Results on 16 cases with whiplash injury,

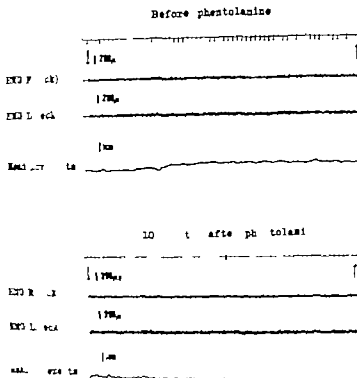


Fig. 7. EMG's from the neck and registrograms of movements of the head of a 30-year-old woman with whiplash injury in the position for Mann test, before and after administration of phentolamine. After injecting this drug intramuscularly there was no significant change in pain in the neck or in the sensation of falling. This was endorsed by the lack of change in either EMG's from the neck or registrograms of movements of the head.

tor depressor propranolol, had the opposite effects on the EMG's, the righting reflex and blindfolded vertical writing. Furthermore, the resulting changes in the EMG's and in equilibrium function caused by administration of drugs affecting the beta receptors were parallel with alterations in the subjects' complaints of neck and vertigo. In contrast to this, administra of drugs affecting the alpha-receptors caused appreciable changes in the EMG's, equili tests or the subjects' complaints. So, these ts show that hypertonicity of the cervical tor muscles in vertigo due to whiplash injury not depend on the activity of alpha recep- . It depends on *over-excitement of beta* ptors in the injured skeletal muscles of the k.

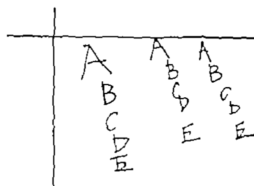
owman & Raper (1967) showed that iso-terenol participates in elevation of muscle ns of denervated slowly contracting skeletal scles through activation of beta receptors. r clinical results seem to be in agreement of is conclusion.

This conclusion is also supported by our results on rabbits (Hinoki & Niki, 1972). To simulate the damage of the neck muscles observed in human subjects with whiplash injury 6% saline solution was injected repeatedly into the deep nuchal muscles of rabbits on one side. Iso-proterenol or noradrenaline was injected into the same site in the nuchal muscles before and after the saline, and the resulting changes in equilibrium function and tonus of the neck muscles were measured by recording eye nystagmus and the EMG simultaneously. The following results were obtained from these experiments.

*(i) After injection of iso-proterenol into the uni*lateral deep nuchal muscles of normal rabbits there was no appearance of nystagmus (or abnormal eye movements) or marked increase in the EMG's from the muscles into which iso-proterenol was injected.

(ii) After about 10 injections of 6% saline solution into the unilateral deep nuchal muscles rabbits sometimes showed moderately elevated

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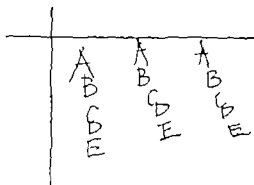


Fig 6 The blindfolded vertical writing tests of a 36-year old woman with whiplash injury before and after administration of noradrenaline. After injecting this drug complaints of pain in the neck and vertigo did not change and there was no significant change in writing.

We tested the effect of noradrenaline on 8 cases with whiplash injury using the EMG the righting reflex test and the blindfolded vertical writing test None of the cases showed any significant change in either the EMG s or the equilibrium tests.

6 *Results on vertigo cases with whiplash injury using phentolamine*

(i) Representative case A 30-year-old woman who had sustained whiplash injury one month before At the time of the accident she was aware of a cracking sound in the neck A few minutes later pain of the left side of the neck, left tinnitus and a sensation of swaying developed X Rays of the neck showed no structural abnormality except a slight incongruence of the cervical vertebrae ($c_{4,5}$). When we injected phentolamine into this woman intramuscularly her complaints did not change. This was endorsed by the results shown in Figs. 7 and 8 That is, the abnormal EMG s from the neck and disturbances of the righting reflex showed no demonstrable changes when this drug was given (Fig. 7) The blindfolded vertical writing test of this subject showed no apparent change in writing after phentolamine was given (Fig. 8).

(ii) Results on 7 cases with whiplash injury We tested the effect of phentolamine on 7 cases with whiplash injury by examining the EMG s and by the equilibrium tests mentioned above. None of the cases tested showed any significant change in either the EMG s or the equilibrium tests.

COMMENT

1 *Remarks on sympathetic induction of hypertonicity of the neck muscles and its contribution to development of vertigo based on clinical and experimental observations*

Many workers have reported that cervical vertigo is due essentially to circulatory disorders of the vertebral artery or of the internal auditory artery originating from irritation of the posterior cervical sympathetic nerve (Barrè, 1926 Lieou 1928 Maspetiol, 1960) However in cases of whiplash injury we often found that there was a close association between complaints, such as neck pain, suggesting hypertonicity of the cervical soft supporting tissues, and various autonomic syndromes and vertigo So we wondered whether hyperstimulation of the autonomic nerves, especially the cervical sympathetic nerve brings about hypertonicity of the cervical muscles and promotes the appearance or intensification of vertigo This idea was supported by the results mentioned above That is, administration of beta receptor stimulant, iso-proterenol, caused an increase in abnormal EMG discharges from the neck muscles in parallel with increased impairment of the righting reflex Similar results were obtained by the blindfolded vertical writing test. That is, when this drug was given ataxia or deviation in writing appeared or was intensified. Whereas administration of the beta recep-

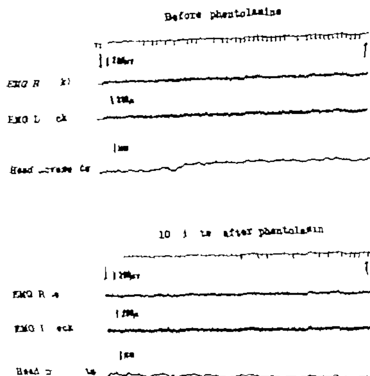


Fig. 7. EMG's from the neck and registrograms of movements of the head of a 30-year-old woman with whiplash injury in the position for Mann's test, before and after administration of phentolamine. After injecting this drug intramuscularly there was no significant change in pain in the neck or in the sensation of falling. This was endorsed by the lack of change in either EMG's from the neck or registrograms of movements of the head.

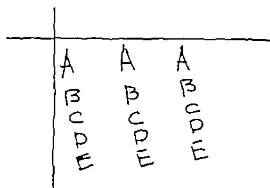
tor depressor propranolol, had the opposite effects on the EMG's, the righting reflex and blindfolded vertical writing. Furthermore, the resulting changes in the EMG's and in equilibrium function caused by administration of drugs affecting the beta receptors were parallel with alterations in the subjects' complaints of neck pain and vertigo. In contrast to this, administration of drugs affecting the alpha-receptors caused no appreciable changes in the EMG's, equilibrium tests or the subjects' complaints. So, these results show that hypertonicity of the cervical erector muscles in vertigo due to whiplash injury does not depend on the activity of alpha receptors. It depends on over-excitement of beta receptors in the injured skeletal muscles of the neck.

Bowman & Raper (1967) showed that iso-proterenol participates in elevation of muscle tonus of denervated slowly contracting skeletal muscles through activation of beta receptors. Our clinical results seem to be in agreement of their conclusion.

This conclusion is also supported by our results on rabbits (Hinoki & Niki, 1972). To simulate the damage of the neck muscles observed in human subjects with whiplash injury 6% saline solution was injected repeatedly into the deep nuchal muscles of rabbits on one side. Iso-proterenol or noradrenaline was injected into the same site in the nuchal muscles before and after the saline, and the resulting changes in equilibrium function and tonus of the neck muscles were measured by recording eye nystagmus and the EMG simultaneously. The following results were obtained from these experiments.

(i) After injection of iso-proterenol into the unilateral deep nuchal muscles of normal rabbits there was no appearance of nystagmus (or abnormal eye movements) or marked increase in the EMG's from the muscles into which iso-proterenol was injected.

(ii) After about 10 injections of 6% saline solution into the unilateral deep nuchal muscles rabbits sometimes showed moderately [illegible]



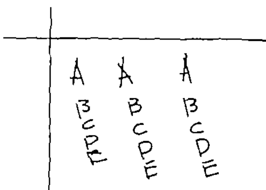


Fig 8 The blindfolded vertical writing tests of a 30-year-old woman with whiplash injury before and after administration of phentolamine. After this drug was injected intramuscularly there was no significant change in complaints of pain in the neck and vertigo. This was endorsed by the lack of change in deviation in writing.

EMG discharges from the neck muscles affected by saline and only slight spontaneous nystagmus. When iso-proterenol was injected into the same site in these muscles, the animals tended to show a marked increase in the EMG s from these muscles and intensification of pre-existing spontaneous nystagmus.

Injection of noradrenaline into the same muscles caused no increase in nystagmus or in muscular discharges.

These results also support our previous idea on vertigo of traumatized patients i.e. over excitement of beta receptors in the injured neck muscles, especially the deep nuchal muscles, can cause hypertonicity of these muscles and this hypertonicity results in vertigo of cervical origin However there has been much discussion as to whether innervation of the sympathetic nervous system affects the tonus of the skeletal muscl exists. Thus, to confirm our idea more definitel we have first to examine the reports on th problem and then to obtain some evidence on th morphological relationship between the sympa thetic nerves and muscle fibers, especially th muscle spindles of the neck muscles.

2. *Reports on the effect of sympathetic innervation on the tonus of skeletal muscles*

Fulton detected a decrease of muscle tonus afte sympathectomy (Fulton, 1928). Popa & Pop also suggested that if the sympathetic pre ganglionic fibers are transected, prolonged muscle hypotonia may result (Popa & Popa 1931). Kuntz and Kerper found that the muscle of the wing of birds are not atonic after section of the dorsal roots of the brachial plexus. However they become atonic after section of both the dorsal roots of the brachial plexus and the cervical sympathetic trunk (Kuntz & Kerper 1926) These findings are very similar to those reported by Hunter (Hunter 1924). Recently Hunt reported that primary sympathetic actions not related to changes in blood flow can be mediated directly to the muscle spindle, presumably through postganglionic sympathetic nerve fibers in the spindle (Hunt, 1960) From this he stressed the possibility of a significant direct i e non-humoral, contribution of the sympathetic nervous system to motor integration via "sympathetic bias" on the muscle spindle, in addition to the "gamma bias"

These findings suggest that there may be a functional relationship between the sympathetic nerves and the somatic proprioceptive reflex arcs in maintenance of muscle tonus. However there is still controversy on this subject. So we must discuss this problem further by examining recent works using new technics before we mention our results. Barker first reported the existence of intrafusal sympathetic innervation, but has recently retracted his view (Barker 1967) Boyd also discredited this possibility (Boyd 1962). Thus, at present this possibility may be neglected. Recently Santini and his group have studied this subject. They made electron microscopic

studies on the tenuissimi and lumbrical muscles of 4 cats, one of which was treated with 5-hydroxydopamine (5-HDA). They found that there are bundles of thin axons (less than 0.5 μ) in the capsular spindle and in the extracapsular polar regions. Following 5-HDA treatment some of these fibers were found to contain large dense vesicles (80 nm) not seen in the other axons of the bundle in semi-serial sections. They also found that after 5-HDA treatment these thin axons with large dense vesicles were seen in bundles which included larger unmyelinated axons, presumably of the gamma type, which are normally devoid of large dense vesicles (Santini & Ibata, 1971). These findings seem to indicate that there is a morphological relationship between the sympathetic postganglionic fibers and the muscle spindles.

3. *Our observations on the morphological relationship between the sympathetic nerves and muscle fibers, particularly the muscle spindles*

To obtain further evidence on this subject, we and Dr Daikoku recently made electron microscopic studies on the deep nuchal muscles of rabbits (Niki et al., 1973). Our results were as follows.

Sensory and motor nerve endings were seen on the surface of intrafusal muscle fibers of the deep nuchal muscles of rabbits, but no indications of sympathetic nerve endings were found. However as shown in Fig. 9 in the perimysium of the muscle spindle, apart from myelinated rve fibers, unmyelinated nerve fibers of 0.3–1.5 diameter could be detected. Granular vesicles these nerve fibers were 900–1200 Å in diameter. In normal rabbits, these nerve fibers rely contain granules and are difficult to tinguish. In the muscle spindle cavity unmyelinated nerve fibers could also be observed. normal rabbits these nerve fibers contain a ery few granules and are difficult to distinguish. However as shown in Fig. 10, unmyelinated erve fibers in the muscle spindle cavity of the njured neck muscles of rabbits with spontaneous nystagmus contain large granules and are more easily detectable. Furthermore, it is, we feel, interesting in relation to innervation of gamma fibers on muscle tonus that these unmyelinated nerve fibers were always detected near to motor nerve endings of intrafusal muscle fibers. There seems to be a certain similarity in nature between the core vesicles described by Santini and Ibata and those described here. Thus, the present findings suggest that there is a morphological relationship between sympathetic nerve fibers and the muscle spindles. Our findings also suggest that there is hyperexcitation of the sympathetic nerve in the muscle spindle of neck muscles after saline injection, because Santini and Ibata showed that the granules in the thin unmyelinated nerve fibers in the capsular spindle are manifested after treatment with 5-HDA (Santini & Ibata, 1971). Of course, further investigations using other examinations, such as formaldehyde-induced fluorescence (Falk–Hillarp method), are necessary to prove definitely whether postganglionic sympathetic nerve fibers connect with the muscle spindles of the neck muscles of rabbits. Furthermore, even if the present findings show that postganglionic sympathetic nerve fibers connect with the muscle spindles, they do not give direct proof that these sympathetic nerve fibers can play a similar role to beta receptors in elevation of muscle tonus. However from our morphological findings described above and our clinical and experimental observations on the effect of drugs acting on the sympathetic receptors, it seems probable that over-excitement of the cervical sympathetic nerves related to the beta receptors in the neck muscles causes abnormal increase in the activity of the proprioceptors of these muscles. Thus, hypertonicity of the neck muscles is produced sympathetically and this in turn results in vertigo of cervical origin.

4. *Neural mechanism of cervical vertigo in relation to sympathetically induced hypertonicity of the neck muscles*

The question then arises of how the hypertonicity thus evoked can induce vertigo of cervical origin. We have been studying central mechanism



Fig 9 Perimysium of the muscle spindle of the deep nuchal muscles of a normal rabbit. In the perimysium, apart from a myelinated nerve fiber (*N*), unmyelinated nerve fibers of 0.5–1.5 μ diameter can be seen. These nerve fibers contain granular vesicles of 900–1200 Å diameter (*n*). The arrows indicate the borders of the perimysium.



Fig 10 Muscle spindle cavity of the injured deep nuchal muscles of a rabbit with spontaneous nystagmus. An unmyelinated nerve fiber contains large granules, seen in the area enclosed in a square in the upper part of this figure. The nerve fiber with these granules is far more easily detectable in the injured deep nuchal muscles of rabbits with spontaneous nystagmus than in those of normal rabbits. The inserted figure shows the granules at higher magnification. *N* myelinated nerve fiber *Nuc* nucleus *Nm* motor nerve endings.

of vertigo due to whiplash injury since 1967. Our opinion on this mechanism has been that there is a close relationship between the tonus of the deep nuchal muscles and the activity of the brain stem and the cerebellum, and that hypertonicity of the deep nuchal muscles and dysfunction of these parts of the brain have a trigger-and-target relationship in bringing about vertigo of cervical origin. However, we proposed this idea from the standpoint of the gamma system (Hinoki et al., 1971). It remained to be determined whether this idea could be applied to interpretation of the mechanism of vertigo due to hypertonicity of the neck muscles by the sympathetic nerves. We tested this in rabbits (Hinoki & Niki, 1972). The effects of drugs and optokinetic stimulation on the EEG, EMG and ENG of the rabbits were examined before and after repeated injections of 6% saline solution into the deep nuchal muscles. The results obtained were as follows.

(i) A normal rabbit showed only slight increase in the EMG's from the deep nuchal muscles and fairly good development of optokinetic nystagmus when iso-proterenol was injected into these neck muscles. In parallel with this, the EEG's from various parts of the brain, such as the hippocampus, the midbrain reticular formation and the neo-cortex, showed a fairly good arousal reaction.

(ii) However, in the same rabbit after repeated injections of 6% saline solution into the deep nuchal muscles, a marked increase in the EMG discharges developed when iso-proterenol was injected. In parallel with this, there was little evidence of optokinetic nystagmus. The EEG's showed that the arousal reaction was inhibited.

These results showed that sympathetically induced hypertonicity of the deep nuchal muscles can cause disorders of the brain stem reticular formation. Its effects on the cerebellum are still unknown.

From these clinical and experimental observations, the mechanism of sympathetically induced vertigo of cervical origin seems to be as follows. After whiplash injury sympathetic nerves related to the beta receptors in the injured neck muscles may become over-excited, and this markedly enhances the activity of the proprioceptors of these muscles. Thus, abnormal centripetal impulses from these receptors may ascend along centripetal paths, such as the spinoreticular tract, and reach the brain stem and the hypothalamus causing dysfunction of these parts of the brain. This dysfunction may be projected to the eyes, the trunk and the limbs through descending paths, such as the reticulospinal tract and the MLF, causing disability or ataxia of these organs. Thus, vertigo is possibly induced by this ataxia or disability. Of course, hypertonicity of the deep nuchal muscles may also have some effect on the activity of the cerebellum, which is one of the important centers of the proprioceptive reflexes. Naturally dysfunction of this part of the brain participates in producing vertigo, in close collaboration with the brain stem.

In addition to these neural mechanisms, we should also take the following mechanism into consideration in assessing vertigo of this type. That is, the dysfunction of the brain stem and the hypothalamus mentioned above may be conveyed to the neck muscles through centrifugal (descending) sympathetic paths, such as Schutz's longitudinal dorsal fascicle and the cervical sympathetic nerves. Thus, tonus of these muscles is increased and this in turn, causes vertigo of cervical origin.

ACKNOWLEDGEMENTS

The authors are greatly indebted to Prof. K. Niimi (Dept. of Anatomy, Okayama Univ.) for valuable advice on fiber connections in the central nervous system and to Prof. S. Daikoku (Dept. of Anatomy, Tokushima Univ.) for collaboration in electron microscopic studies on skeletal muscle fibers. The assistance and helpful discussions of other members of the ENT Department of Tokushima University are gratefully acknowledged.

ZUSAMMENFASSUNG

Um die Richtigkeit der Hypothese zu beweisen, dass die Überreizbarkeit des zervikalen Sympathikus-Nervensystems eine Ursache der Hypertonie des Weichteils der Halsgegend, besonders der tiefen Nackenmuskeln, ist und dass diese Hypertonie eine Ursache des traumatischen Schwindels ist, wurde bei 44 schleudertraumatischen

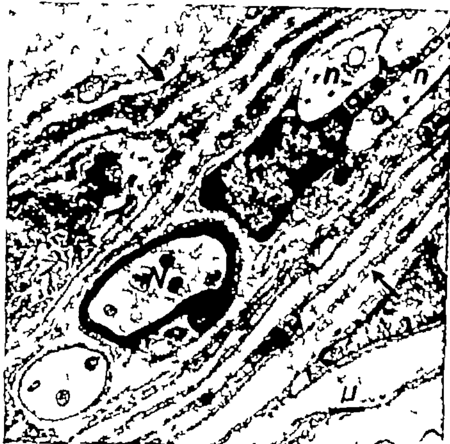


Fig 9 Perimysium of the muscle spindle of the deep nuchal muscles of a normal rabbit. In the perimysium, apart from a myelinated nerve fiber (*N*), unmyelinated nerve fibers of 0.5–1.5 μ diameter can be seen. These nerve fibers contain granular vesicles of 900–1200 Å diameter (*n*). The arrows indicate the borders of the perimysium.



Fig 10 Muscle spindle cav ty of the njured deep nuchal muscles of a rabbit with spontaneous nystagmus. An unmyelinated nerve fiber contains large granules, seen in the area enclosed in a square in the upper part of this f gure. The nerve fiber with these granules is far more easily detectable n the injured deep *nuchal muscles of rabbits with* spontaneous nystagmus than in those of normal rabbits. The inserted figure show the granules at higher magnification. *N* myelinated nerve f ber *Nuc*, nucleus *Nm*, motor nerve endings.

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LUMBOMUSCULAR PROPRIOCEPTIVE REFLEXES IN BODY EQUILIBRIUM

Manabi Hinoki and Nobuya Ushio

From the Department of Otolaryngology, School of Medicine, Tokushima University, Tokushima, Japan

Abstract. To evaluate the role of reflexes related to the lumbar proprioceptors in maintenance of body equilibrium, changes in equilibrium function of the eyes and body were observed after unilateral procainization of the lumbar erector muscles. Observations were made on normal subjects and vertigo cases with lumbar pain after whiplash injury using various equilibrium tests. The results obtained were as follows.

(1) On unilateral procainization of the lumbar erector muscles of normal subjects, eye nystagmus and disturbances of the righting reflex developed. Simultaneously changes in drift reactions of the lower limbs were detected by the stepping test. Namely in many of the subjects examined the direction of stepping deviation became quite different from that before procainization, and stepping after procainization tended to show slight or moderate ataxic features, associated with sensation of unsteadiness.

(2) When procaine was injected unilaterally into tender spots in the lumbar erector muscles of traumatic vertigo cases, spontaneous eye nystagmus and disturbances of the righting reflex decreased. Simultaneously significant changes in the drift reactions of the lower limbs were observed in many of the cases examined. Namely the direction of deviation became the opposite of that before procainization and ataxia in walking almost disappeared with reduction in vertigo.

The following conclusions were drawn from these findings.

(1) The effects of procaine on equilibrium of normal subjects are in sharp contrast to its effects on equilibrium in traumatic vertigo cases. Findings in the former might be due to increased imbalance between the activities of the right and left lumbar proprioceptors, while those in the latter might be due to decreased imbalance between the two.

(2) These findings support the view that from the standpoint of body equilibrium, there are two phases of the proprioceptive reflex, and that Fukuda's concept of two phases of the labyrinthine reflex, i.e. a stage of disturbance and a stage of coordination, can be applied to interpretation of the proprioceptive reflex of lumbar origin.

Using newly devised vestibular tests, i.e., the blindfolded vertical writing test and the stepping test Fukuda showed that eye and body reflexes induced by labyrinthine stimulations, such as rotation and calorization, vary significantly according to the magnitude or intensity of labyrinthine stimuli given and the ability of subjects to react to these stimuli. Thus, he introduced the new idea that there are two phases of the labyrinthine reflex from the standpoint of body equilibrium, i.e., the stage of disturbance and the stage of coordination (Fukuda, 1958). The former stage is produced by intense labyrinthine stimulation, which causes a marked vestibular imbalance, and includes disturbances of bodily equilibrium reflexes as well as experimental eye nystagmus, an important sign of disturbed labyrinthine function. At this stage labyrinthine reflexes overwhelm the power of the will and consequently disrupt normal regulation of the entire body musculature by the will, which results in ataxia of the eyes and body. Thus, vertigo of labyrinthine origin is produced. The stage of coordination was described vaguely under the name of "latent nystagmus" or *Nystagmusbereitschaft.* This stage is induced by mild or adequate labyrinthine stimulation, which causes a slight vestibular imbalance, and includes neither disturbances of the righting reflex nor experimental eye nystagmus. However at this stage there is still a drift phenomenon of the limbs, the direction of which is the same as that of the rapid component of nystagmus which would be elicited if stronger labyrinthine stimulation were applied. Furthermore, these drift phenomena do not show any ataxic features. Based on these findings, Fukuda pointed out that at this stage the vestibular labyrinth acts to help the will in regulating the entire body muscu-

Fällen die Gleichgewichtsfunktion und die EMG-Entladung von Nackenmuskeln vor und nach der Injektion der die Sympathikus-Rezeptoren beeinflussenden Substanz gemessen.

Folgende Resultate wurden erzielt.

1) Die Injektion von Iso-Proterenol (Beta Rezeptor stimulierende Substanz) verursachte sowohl die Verstärkung der Störung des Stellreflexes als auch eine bedeutende Zunahme der EMG-Entladungen verletzter Nackenmuskeln. Beim Vertikalschreibversuch (Fukuda) wurde das Auftreten oder die Zunahme der Ataxie und des Abweichens der Schriftzeichen bemerkt, während die Injektion von Propranolol (Beta-Rezeptor unterdrückende Substanz) die EMG-Entladungen, den Stellreflex und das Vertikalschreiben entgegengesetzt beeinflusste. Ausser dem verlief die in EMG und in der Gleichgewichtsfunktion eingetretene Veränderung mit der der Beschwerde der Versuchsperson, d. h., mit der Änderung des Nackenschmerzes und des Schwindels, parallel.

2) Die Alpha Rezeptor beeinflussende Substanz, z. B. Noradrenalin (Alpha-Rezeptor stimulierende Substanz) oder Phentolamin (Alpha Rezeptor unterdrückende Substanz) hatte keine bemerkenswerte Wirkung auf EMG und die Gleichgewichtsfunktion oder auf die Beschwerde der Versuchsperson.

Diese Ergebnisse zeigen bei einem durch das Schleuder trauma verursachten Schwindel, dass die Hypertonie der Nackenmuskeln sympathisch hervorgerufen wird, und dass diese Hypertonie, die die Ursache des von dem Nacken ausgehenden Schwindels ist, in der Übererregbarkeit von Beta Rezeptoren der verletzten Nackenmuskeln ihren Grund hat.

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can be temporarily blocked by direct procainization of the muscle (Walshe, 1924, Shimazu, 1959). Therefore, in this series of examinations we procainized the lumbar erector muscles directly and carried out various kinds of equilibrium tests before and after procainization. Preliminary studies on the effect of procaine on the EMG showed that the proprioceptors in the lumbar erector muscles were blocked most effectively after 10 minutes, and that blocking lasted for about 60 minutes. Accordingly equilibrium examinations were started 10 minutes after procaine injection. A needle was inserted into the lumbar erector muscles on one side at the level of $L_4 - L_5$ to a depth of 4 cm and 7.5–10.0 ml of procaine were injected. In normal subjects procaine was injected into the right lumbar erector muscles, while in traumatized patients the injection was given on the side on which lumbago existed or was greatest.

3. *Equilibrium Test Used*

All the subjects were examined by equilibrium tests and by routine neurological examinations and hearing tests. However this paper mainly reports results of equilibrium tests, i.e., tests of the righting reflex, a test for the drift phenomenon of the lower limbs and a test for spontaneous nystagmus. The righting reflex was examined using Mann's test and "the dynamic righting reflex test" (Ushio, 1970). The latter test was specially devised to detect disturbances of the righting reflex due to dysfunction of the lumbar proprioceptors. In this test the subject is asked to change from the upright position to the right lateral position (see *a*, *b* in Fig. 1), from the right lateral position to the upright position (see *c*, *d* in Fig. 1), from the upright position to the left lateral position (see *a*, *b* in Fig. 1) and from the left lateral position to the upright position (see *c*, *d* in Fig. 1), and to maintain each of the positions for about 5 seconds. The right and left lateral positions are those at which the subject's trunk is bent at an angle of about 30° at the pelvis. Usually the subject keeps his eyes open and the test is repeated 5 times. Changes in righting function are observed by recording head movements using a strain-gage-type instrument. The drift phenomenon of the lower limbs was tested by Fukuda's stepping test (Fukuda, 1958). The test for spontaneous nystagmus was carried out in Mann's position with the subject's eyes open and closed, recording the ENG.

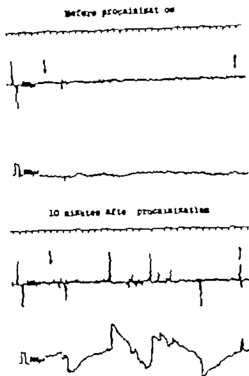


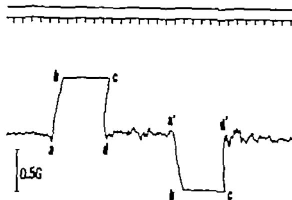
Fig. 2. ENG's of normal 20-year-old man in Mann position with the eyes closed, before and after procainization. After procainization he showed horizontal nystagmus of small and medium amplitude, with jerks to the right and left.

4. *Effects of Procainization of the Lumbar Erector Muscles of Normal Subjects and Traumatized Patients*

1. *Results on normal subjects*

(i) *Representative cases.* Case 1. A normal 20-year-old man. Procaine was injected into the right lumbar erector muscles. After procainization he did not develop vertigo when he stood still with his eyes open or show demonstrable distrubances of the righting reflex in Mann's test. However the dynamic righting reflex test revealed a significant swaying of the body

Before procai ization



10 mi tes afte procai ization

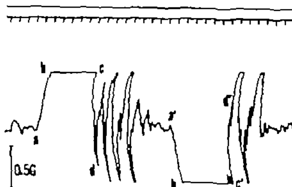


Fig 1 Head movements of a normal 20-year-old man in the dynamic righting reflex test, before and after unilateral procainization of the lumbar erector muscles. *After procainization swaying of the body (head) developed*, associated with a sensation of falling, particularly on changing to the upright position from the right and left lateral positions.

lature and consequently to promote static and dynamic equilibrium in human subjects. This concept was found to be useful in analyzing the characteristics of aural vertigo For instance, Hinoki found that the labyrinthine reflexes dur ing the attack period of Ménière s disease correspond to those in the stage of disturbance, while the labyrinthine reflexes in the interval are very similar to those in the stage of coordination (Hinoki 1959) These findings indicate that Fukuda s concept is available in understanding not only the physiology of the vestibular labyrinth, but also vertigo induced by this organ.

The question arises of whether this concept holds in analysis of other kinds of vertigo or disequilibrium. There is some evidence that traumatic cases with vertigo and neck pain often show disequilibrium of the eye and body such as spontaneous eye nystagmus, disturbances of the righting reflex and drift reactions of the limbs with ataxic features In these cases, amelioration of vertigo and neck pain tends to be accompanied by a significant reduction in disturbances of the righting reflex and dis appearance or decrease in spontaneous eye nystagmus. In parallel with this, drift phenomena of the limbs become opposite in direction and *ataxic features are reduced or abolished Similar* findings were sometimes observed in cases with whiplash injury who showed vertigo and lumbar *pain. So we wondered if Fukuda s concept could* also be applied in analyzing the characteristics of vertigo of proprioceptive origin

The present work on normal subjects and traumatized patients with vertigo of lumbar origin was to test this possibility

EXPERIMENTAL

1 *Subjects Examined*

In all 21 normal subjects aged 20 to 30 and 22 subjects with whiplash injury aged 20 to 46 were examined using the various equilibrium tests described below The cases with whiplash injury did not include cases in which the head had struck a solid object So none of them showed serious brain damage. However all of them showed vertigo (mostly non-rotatory) and unilateral or predominantly unilateral lumbago

2. *Method of Procaini-ation of the Lumbar Erector Muscles*

It is widely believed that the muscle spindles control the tonus of the skeletal muscles. Recent investigations showed that the activity of the muscle spindles is governed by fine efferent fibers, the gamma fibers. According to Matthews & Rushworth, these nerve fibers have low por caine tolerance and their activity is markedly disturbed by procaine at a time before the activities of the motor (alpha) and sensory nerve fibers are seriously affected (Matthews & Rush worth 1957) Furthermore it has been shown that *the activity of gamma fibers in a muscle*

9 subjects (42.9 %) showed no notable disturbances of the righting reflex.

3 Results on the stepping test Among the 21 normal subjects examined, 13 (61 9 %), who had shown rotational deviation of the body either to the right or to the left, showed a change in direction of deviation of stepping after procainization of the right lumbar erector muscles. Six (46.1 %) of these 13 subjects also developed ataxic walking. Two subjects who showed forward displacement in the stepping test, developed backward displacement with ataxic features after procainization. The remaining 6 subjects showed no significant change in the stepping test after procainization. Furthermore, development of ataxic walking was accompanied by a sensation of falling in many of the subjects examined. With regard to the relationship between the direction of deviation caused by procainization and the side of injection of procaine the following facts were found. Eight (61.5 %) of the 13 subjects developed rotational deviation of the body to the right and 5 (38 5) developed it to the left.

(iii) *Correlation between development of nystagmus and changes in the righting reflex on unilateral procainization of the lumbar erector muscles* Among 12 normal subjects who showed disturbances of the righting reflex on unilateral procainization of the lumbar erector muscles, 10 (83 3) developed eye nystagmus and 2 (16.7) developed neither nystagmus nor abnormal eye movements. Whereas among 9 normal subjects who showed no sign of disturbances of the righting reflex on procainization, 5 (55 6 %) showed nystagmus and 4 (44.4 %) showed neither nystagmus nor abnormal eye movements. That is, after procaine injection spontaneous nystagmus developed more often in subjects showing impairment of the righting reflex than in those who did not.

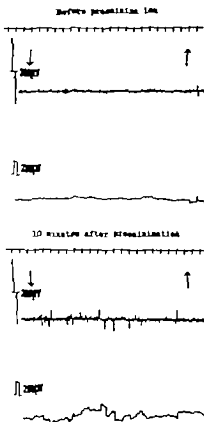


Fig 5 ENG of normal 22-year-old man in Mann's position with the eyes closed, before and after procainization. After procainization he showed horizontal nystagmus of small amplitude, with jerks to the right and left.

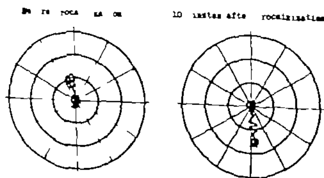


Fig 6. Drift reaction of the lower limbs of a normal 22-year-old man in Fukuda's stepping test, before and after procainization. After procainization marked backward displacement with ataxic features developed, associated with sensation of falling backwards. The deviation in direction and way of walking were opposite before and after procainization.

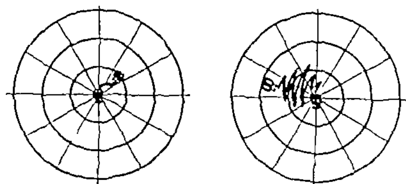


Fig 3 Drift reaction of the lower limbs of a normal 20-year-old man in Fukuda's stepping test, before and after procainization. After procainization marked deviation to the left with ataxic features developed, associated with a sensation of falling to the left. The deviation in stepping and way of walking were opposite before and after procainization.

associated with a sensation of falling, particularly when he changed to the upright position from the right or left lateral position (see *1 d'* in Fig. *1*). *He also* developed horizontal nystagmus of small and medium amplitude to the right and *left respectively* in Mann's position with his eyes closed (Fig. 2) The stepping test showed marked deviation to the left with ataxic features, associated with a sensation of falling to the left *(Fig. 3)* It is worth noting that the direction of deviation and way of walking in the stepping test before and after procainization were quite different

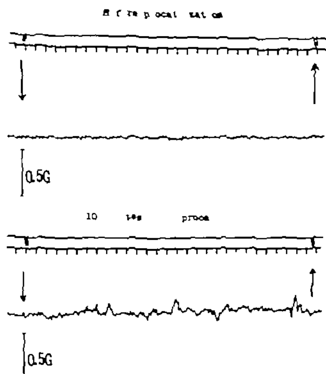


Fig 4 Head movements of a normal 22 yea -old man in Mann's test, before and after *unilateral procainization of* the lumbar erector muscles. After procainization significant swaying of the head developed, associated with unsteadiness of the body

Case 2 A normal 22 year-old man. Procaine was injected into his right lumbar erector muscles. After procainization he developed unsteadiness of the body which increased during the stepping test This was endorsed by the results of Mann's test and the stepping test. That is, as shown in Fig. 4 swaying of the body (head) was detected by Mann's test after procainization The stepping test showed backward displacement with ataxic features after procaine *injection In this case also the direction of deviation* and way of walking in the stepping test before and after procainization were quite different (Fig. 6) This case also developed horizontal nystagmus of small amplitude and showed nystagmus directed to the right and left (Fig. 5)

(ii) *Over-all results in all cases* 1 Results on the spontaneous nystagmus test Spontaneous nystagmus developed in 15 (71 4) of the 21 normal subjects examined after unilateral (right side) procainization of the lumbar erector *muscles and in all these nystagmus was horizon*tal Among these 15 subjects one subject showed nystagmus to the right and 3 subjects showed nystagmus to the left The remaining 11 subjects developed nystagmus directed to both the right and left Six subjects showed neither nystagmus nor abnormal eye movements.

2 Results on the righting reflex tests After procainization disturbances of the righting reflex were observed in *12 (57 1) of the 21 normal* subjects examined either by Mann's test or by the dynamic righting reflex test The remaining

9 subjects (42.9 %) showed no notable disturbances of the righting reflex.

3. Results on the stepping test. Among the 21 normal subjects examined, 13 (61.9 %), who had shown rotational deviation of the body either to the right or to the left, showed a change in direction of deviation of stepping after procainization of the right lumbar erector muscles. Six (46.1 %) of these 13 subjects also developed ataxic walking. Two subjects who showed forward displacement in the stepping test, developed backward displacement with ataxic features after procainization. The remaining 6 subjects showed no significant change in the stepping test after procainization. Furthermore, development of ataxic walking was accompanied by a sensation of falling in many of the subjects examined. With regard to the relationship between the direction of deviation caused by procainization and the side of injection of procaine the following facts were found. Eight (61.5 %) of the 13 subjects developed rotational deviation of the body to the right and 5 (38.5 %) developed it to the left.

(iii) *Correlation between development of nystagmus and changes in the righting reflex on unilateral procainization of the lumbar erector muscles.* Among 12 normal subjects who showed disturbances of the righting reflex on unilateral procainization of the lumbar erector muscles, 10 (83.3 %) developed eye nystagmus and 2 (16.7 %) developed neither nystagmus nor abnormal eye movements. Whereas among 9 normal subjects who showed no sign of disturbances of the righting reflex on procainization, 5 (55.6 %) showed nystagmus and 4 (44.4 %) showed neither nystagmus nor abnormal eye movements. That is, after procaine injection spontaneous nystagmus developed more often in subjects showing impairment of the righting reflex than in those who did not.

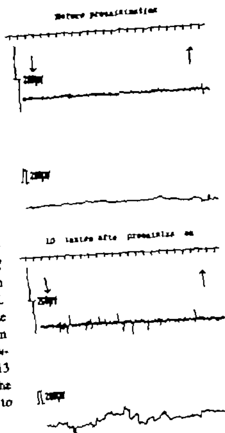


Fig. 5. ENG's of a normal 22-year-old man in Mann position with the eyes closed, before and after procainization. After procainization he showed horizontal nystagmus of small amplitude, with jerks to the right and left.

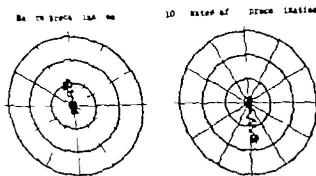


Fig. 6. Drift reaction of the lower limbs of a normal 22-year-old man in Fukuda stepping test, before and after procainization. After procainization marked backward displacement with ataxic features developed, associated with a sensation of falling backwards. The deviation in direction and way of walking were opposite before and after procainization.

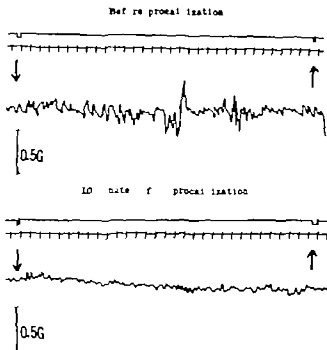


Fig 7 Head movements of a 45-year-old man with whiplash injury in Mann s test, before and after unilateral procainization of tender spots in the lumbar erector muscles. After procainization the sensation of falling and lumbar pain decreased significantly In parallel with this, disturbances of the righting reflex also decreased.

(iv) *Correlation between development of nystagmus and changes in stepping on unilateral procaini ation of the lumbar erector muscles* Among the 15 normal subjects who showed a change either in the direction of deviation or in the way of walking in the stepping test after procaine injection 13 (86 7 %) showed nystagmus and 2 (13 3) showed neither nystagmus nor abnormal eye movements. Whereas among 6 normal subjects who did not show any notable changes in stepping after procaine injection, 2 (33 3 %) developed nystagmus and 4 (66 7 %) developed neither nystagmus nor abnormal eye movements. That is, after procaine injection spontaneous nystagmus developed *more often* in subjects showing a change in stepping than in those who did not

2. *Results on traumatized patients*

(i) *Representative cases* Case 3 A 45-year-old man who had sustained a whiplash injury 4 months previously when his car was struck by another vehicle Immediately after the impact he did not show any notable brain symptoms, such as loss of consciousness and was not aware of any blow on the head However 24 hours after the accident he developed stiffness of the neck and nausea. Ten days after the accident pain of the waist developed associated with a sensation of falling, a dull feeling and bilateral tinnitus. These complaints are still present and are associated with the weather X Rays of the neck and waist showed no structural abnormality When procaine was injected into the right lumbar erector muscles, he reported reduction in the sensation of falling and in lumbar pain In parallel with this, disturbances of the righting reflex and spontaneous nystagmus apparently improved That is, as shown in Fig. 7 a marked decrease in swaying of the body was observed in Mann s test. He also showed a significant reduction in spontaneous nystagmus, which before procainization was marked and was directed to the right and left (Fig. 8) Moreover as shown

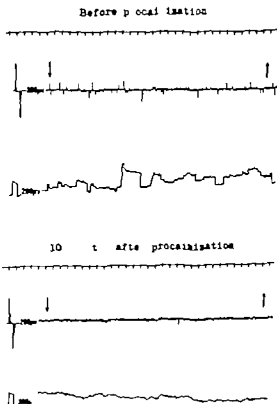


Fig 8 ENG s of a 45-year-old man with whiplash injury in Mann position w th the eyes closed, before and after procainization. After procainization his spontaneous nystagmus directed to the right and left decreased significantly

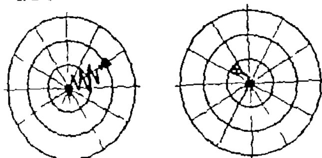


Fig. 9. Drift reaction of the lower limbs of a 45-year-old man with whiplash injury in Fukuda's stepping test, before and after procainization. After procainization deviation in stepping changed in direction and ataxic features disappeared.

in Fig. 9 the direction of deviation in the stepping test became reversed and ataxic features were lost.

Case 4. A 32 year-old man who received a whiplash injury when his car was bumped from the rear. Immediately after the impact he was dazed for a few minutes, but he was not aware of any memory defect or blow on the head. About five hours after the accident he complained of stiffness of the neck and a dull feeling. Two weeks after the accident he developed a sensation of falling and pain of the waist (particularly on the right side). X Rays of the neck and waist showed no structural abnormality. On procainization of tender spots (right side) in the lumbar erector muscles, he reported reduction in the sensation of falling and in lumbar pain. In parallel with this, impairment of the righting reflex and spontaneous nystagmus improved. That is, as shown in Fig. 10, a marked decrease in swaying of the body was observed in Mann's test. He also showed significant reduction in spontaneous nystagmus (see Fig. 11). Moreover, as shown in Fig. 12, after procainization deviation in the stepping test changed in direction to forward displacement and ataxic features were lost.

(ii) Over-all results in all cases. 1. Results on the spontaneous nystagmus test. Among 22 cases with whiplash injury 16 (72.7 %) showed spontaneous nystagmus before procainization. Ten (62.5 %) of the latter showed either disappearance or reduction of spontaneous nystagmus after procaine injection on the side on which lumbago existed or was greatest. The other 6 cases (37.5 %) still developed spontaneous nystagmus even after procainization.

2. Results on the righting reflex tests. The 22 traumatized patients all showed disturbances of the righting reflex before procainization. Among these, 17 (77.2 %) showed either disappearance or reduction in disturbances of the righting reflex after procainization, while in 5 (22.8 %) the disturbances were unchanged.

3. Results on the stepping test. Before procainization, 15 (68.2 %) of 22 cases with whiplash injury showed rotational stepping deviation either to the right or to the left, and 4 (18.2 %) showed backward displacement in stepping. The remaining 3 (13.6 %) showed neither rotational deviation nor displacement in the stepping test. Furthermore, in 19 cases rotational deviation or backward displacement in the stepping test was accompanied by ataxia in walking. On unilateral procainization of tender spots in the lumbar erector muscles, the direction of deviation of stepping of 12 (80.0 %) of the 15 cases with rotational deviation became reverted and ataxia in walking decreased. Four cases with backward displacement in the stepping test all developed forward displacement after procainization and ataxia in walking almost disappeared. The above 3 cases who showed neither rotational deviation nor backward displacement developed no significant change in the stepping test after procainization. Furthermore, reduction in ataxia in walking was parallel with decrease in either a sensation of falling or unsteadiness of the body during stepping.

With regard to the relationship between the

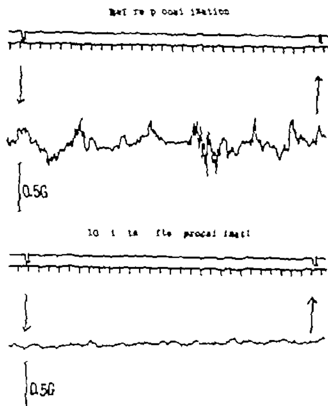


Fig 10 Head movements of a 32 year-old man with whiplash injury in Mann s test, before and after unilateral procainization of tender spots in the lumbar erector muscles. After procainization his sensation of falling backwards and lumbar pain decreased significantly and in parallel impairment of the righting reflex also decreased.

direction of deviation caused by procainization and the side of injection of procaine 8 (66 7 %) of the 12 cases with rotational stepping deviation developed deviation to the side of procainization and 4 (33 3 %) to the other side

(iii) *Correlation between changes in spontaneous nystagmus and in the righting reflex after unilateral procainization of tender spots in the lumbar erector muscles* Among 17 traumatized patients who showed reduction in disturbances of the righting reflex on procainization of tender spots in the unilateral lumbar erector muscles, 8 (47 1 %) showed either disappearance or decrease and 4 (23 5 %) showed no change in spontaneous nystagmus. The remaining 5 (29 4 %) did not show spontaneous nystagmus either before or after procainization Among 5 traumatized patients who did not show any demonstrable changes in disturbances of the righting reflex following procaine injection 2 (40 %) showed either disappearance or decrease in spontaneous nystagmus and 2 (40 %) showed no change in it. The remaining case (20 %) showed no spontaneous nystagmus before or after procainization That is after unilateral procainization of tender spots in the lumbar erector muscles pre-existing spontaneous nystagmus decreased more in cases showing reduction in impairment of the righting reflex than in those who did not.

(iv) *Correlation between changes in spontaneous nystagmus and in stepping after procainization of tender spots in the unilateral lumbar erector muscles* Among 15 traumatized patients who showed changes in stepping, either as regard the direction of deviation or the way of walking after procainization 8 (53 3 %) showed reduction and 3 (20 0 %) showed no change in pre-existing nystagmus. The remaining 4 (26 7 %) showed no

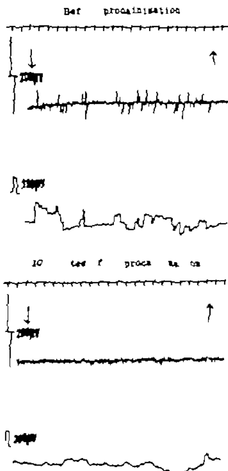


Fig 11 ENG s of a 32 year-old man with whiplash injury i Mann s position with the eyes closed, before and after procainization. After procai ization his spontaneous nystagmus directed to the right and left decreased significantly

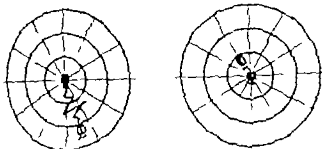


Fig. 12. Drift reaction of the lower limbs of a 31-year-old man with whiplash injury in Fukuda's stepping test, before and after procainization. After procainization the direction of deviation changed to forward displacement and ataxic gait almost disappeared.

tus of nystagmus either before or after procainization. Whereas among 7 traumatized patients who showed no demonstrable change in the stepping test after procainization, 3 (42.8 %) showed reduction and 3 (42.8) showed no change in spontaneous nystagmus. The remaining case (14.3) showed no nystagmus before or after procainization. That is, after procaine injection pre-existing spontaneous nystagmus decreased more often in traumatized patients showing a change in stepping than in those who did not.

COMMENT

1. *The phases of the proprioceptive reflex of lumbar origin from the standpoint of body equilibrium, with special reference to Fukuda's "concept of two phases of the labyrinthine reflex"*

The following facts were noted from the above series of examinations

1. On procainization of the unilateral lumbar erector muscles of normal subjects, eye nystagmus and disturbances *of the righting reflex* developed. At the same time, changes in the drift reaction of the lower limbs were detected by the stepping test. Namely in many of the subjects examined the direction of deviation in stepping became opposite to that before procainization, and stepping after procainization tended to show slight or moderate ataxic features, associated *with a sensation of falling.*

2. Wh rocaine was injected unilaterally into tender spots in the *lumbar erector muscles of traumatic vertigo cases*, spontaneous nystagmus and disturbances of the righting reflex decreased. At the same time, significant changes in drift reaction of the lower limbs were observed in many *of the cases examined. Namely* the direction of deviation of stepping became the opposite of that before procainization and after procainization ataxia in stepping almost disappeared in parallel with reduction in vertigo.

Hinoki & Kurosawa have already pointed out that when procaine was injected unilaterally into either the deep nuchal muscles or the sternocleido-mastoid muscles of normal subjects, the subjects developed vertigo, as *indicated by a sensation of falling,* without any sign of cochlear symptoms (Hinoki & Kurosawa, 1964). This was accompanied by disturbances of the righting reflex, and also by drift reactions of the upper limbs (i.e., deviation in writing in the blindfolded vertical writing test). With the lapse of time after the injection the vertigo decreased in parallel with reduction in impairment of the righting reflex. At this stage the subjects still showed deviation in writing, but the direction of deviation was opposite to that soon after procainization. This finding is essentially similar to those obtained from the present examinations. Accordingly we may say that from the standpoint of body *equilibrium there are two phases* of the proprioceptive reflex. One *is the reflex* pattern in which disturbances of the righting reflex and spontaneous nystagmus exist, associ*ated with drift reactions of the limbs with ataxic*

features The other is that in which drift reactions of the limbs become opposite in direction and there are no signs of ataxic features. Of course, in this pattern, no impairment of the righting reflex or spontaneous nystagmus is found Based on the action of procaine on gamma fibers in the muscle, we may assume that the former reflex pattern is due to a marked functional imbalance between the right and left proprioceptors of the neck or waist while the latter is due to a slight functional imbalance between the two From the standpoint of body equilibrium, these findings are important in showing the essential similarity between the patterns of the proprioceptive reflexes of lumbar origin, just mentioned and those of labyrinthine origin initially reported by Fukuda (Fukuda 1958).

From these facts we may say that Fukuda's concept is applicable not only in understanding the characteristics of the labyrinthine reflexes, but also in analyzing those of the proprioceptive reflexes. Furthermore these findings are also helpful in explaining changes in ataxia of lumbar proprioceptive origin during treatment Without this idea, changes in drift reactions of the limbs seem too complicated to be explained uniformally although changes in disturbances of the righting reflex and in spontaneous nystagmus can be explained comparatively easily Now the various patterns of the proprioceptive reflexes related to bodily equilibrium can be explained by introducing the idea of "a stage of disturbance and a stage of coordination" initially proposed by Fukuda in relation to labyrinthine reflexes. The present work is we feel valuable in this respect

2 *Nystagmus due to dysfunction of the lumbar proprioceptors*

We have already reported that when the unilateral neck muscles, especially the deep nuchal muscles of rabbits were paralyzed by procaine or activated by electric stimulation animals often developed *spontaneous nystagmus*. This nystagmus can be induced in rabbits without a labyrinth. But no nystagmus can be observed on unilateral procainization of the superficial nuchal muscles of normal rabbits (Fukui 1971 Ishida, 1972) Igarashi and his co-workers also induced nystagmus of this type in monkeys (Igarashi et al 1969) However there have been no systematic observations on whether nystagmus of this type can be induced from the lumbar erector muscles in human subjects. Yoshii and his co-workers reported that several cases, suffering from tuberculous caries of the thoracic and lumbar spines, developed positional nystagmus associated with positional vertigo But, they did not report that these cases showed spontaneous nystagmus (Yoshii et al 1960) Yamada & Hinoki found that cases with thoracic and lumbar scoliosis sometimes developed spontaneous nystagmus associated with asymmetric EMG's from the lumbar region and that decrease in these EMG's on wearing an active corrective plaster jacket was parallel with reduction in spontaneous nystagmus (Yamada & Hinoki, 1968) These findings suggest that spontaneous nystagmus can be induced by functional imbalance between the right and left lumbar proprioceptors. However there is no definite evidence as to whether nystagmus of this type can be induced in normal subjects on unequal suppression or excitation of the lumbar proprioceptors. Furthermore apart from the two groups of diseases just mentioned it is unknown what kinds of diseases can cause nystagmus of lumbar origin So it is, we feel, valuable to have clarified the fact that spontaneous nystagmus can be induced in normal subjects on unilateral procainization of the lumbar erector muscles. It is also interesting that traumatized patients with unilateral or predominantly unilateral lumbago often developed spontaneous nystagmus, and that this nystagmus decreased significantly or disappeared after unilateral procainization of tender spots in the lumbar erector muscles. Incidentally the nystagmus induced in normal subjects was usually horizontal, and was also usually a mixed type of nystagmus in which the nystagmus varied significantly in the two directions and the eyes jerked to the right and left This of course, differs appreciably from nystagmus of labyrinthine or optokinetic origin

3. *Neural mechanism of development of two phases of the proprioceptive reflex of lumbar origin, with special reference to cerebellar function*

The question then arises of what parts of the brain are closely related with production of two phases of the proprioceptive reflex of lumbar origin. We have already reported that dysfunction of the central nervous system, especially the brain stem and the cerebellum is important in producing vertigo of cervico-lumbo-muscular origin (Ushio, 1971 Hinoki, 1972). Of the two the cerebellum plays the major role in the development of vertigo of lumbar origin. So we wondered if this part of the brain could be especially related with development of two phases of the proprioceptive reflex. In connection with this possibility the following facts seem noteworthy

1 As described above, on unilateral procainization of the lumbar erector muscles of normal subjects, the subjects often developed spontaneous nystagmus as well as bodily ataxia, as indicated by disturbances of the righting reflex and drift reactions of the lower limbs with ataxic features. Cerebellar ataxia, such as dismetria or diadochokinesis of the hands appeared at the same time and its development was well correlated with the development of disequilibrium of the eyes and body

2. Unilateral procainization of tender spots in the lumbar erector muscles of traumatized patients often produced the opposite effects to those in normal subjects. Namely it caused reduction in both spontaneous nystagmus and disturbances of the righting reflex. Drift reactions of the lower limbs became opposite in direction and ataxic features decreased after procainization. At the same time, cerebellar ataxia decreased in parallel with reduction in impairment of the righting reflex and changes in the drift reactions of the lower limbs. However this decrease in cerebellar ataxia was not very closely correlated with reduction in spontaneous nystagmus.

From these findings we may conclude that there is a close correlation between changes in bodily equilibrium, such as the righting reflex and drift reactions of the lower limbs, and changes in cerebellar function. This means that two phases of the proprioceptive reflex of lumbar origin, particularly those related to bodily equilibrium depend greatly on cerebellar function. This idea is compatible with findings of fiber connections of the central nervous system. That is, the lumbar proprioceptors are closely connected to the cerebellum through centripetal paths, such as the posterior spinocerebellar tract. Of course, the brain stem may also be related with changes in bodily reflexes caused by procainization of the lumbar erector muscles, because the lumbar proprioceptors are also connected to the brain stem through centripetal paths, such as the spinoreticular tract. However the intimate correlation between changes in bodily equilibrium and those in cerebellar function in these cases suggest that the cerebellum is more important than the brain stem in development of two phases of the proprioceptive reflex, particularly those related to bodily equilibrium.

From the neuroanatomical point of view the cerebellum may also affect development of spontaneous nystagmus, because the flocculonodular lobe of the cerebellum is known to be important in producing nystagmus. Recently Kornhuber & Sakata reported that lesions of the intermediate part of the vermis, particularly the fastigal nucleus, can produce nystagmus, because this nucleus is closely connected to the brain stem reticular formation and the vestibular nuclei (Kornhuber 1968 Sakata, 1971). Using cats, Eager reported that the posterior spinocerebellar tract terminates in the homolateral anterior lobe of the cerebellum and connects to the fastigal nucleus (Eager 1963). According to Niimi, Eager's findings seem compatible with those in human beings (Niimi, 1973*a*). Thus, centripetal impulses from the lumbar proprioceptors affect eye reflexes through the neural elements just mentioned. However after procainization the correlation between changes in eye reflexes, particularly spontaneous nystagmus and those in cerebellar function was less obvious than the correlation between changes in bodily

Ushio, N 1971 Lumbar pain and cerebellar ataxia as related to vertigo due to whiplash injury *Pract Otol* (Kyoto) *64* 699

Walshe, F M R. 19 4 Observations on the nature of the muscular rigidity of paralysis agitans and its relationship to tremor *Brain 47* 159

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1 Einleitung

Der endemische Kretinismus in Zusammenhang mit Hör- und Sprachstörungen ist seit langem bekannt und hat immer wieder Diskussionen entfacht, inwieweit und ob überhaupt der Schilddrüse eine Bedeutung für die normale Entwicklung des Ohres zukommt. Ist es doch eine Tatsache, dass die Verbreitung der Gehörstörungen weder mit der Häufigkeit des endemischen Kretinismus noch mit der Intensität der Kropfendemie parallel geht (Trotter 1960, Greenwald, 1960, Costa und Ferraris 1963). Erste Beschreibungen derartiger Krankheitsbilder gehen in frühe Zeitepochen zurück. So berichten römische Autoren über den Alpenkropf (Juvenal und Virtuv). Im 16. und 17. Jahrhundert weisen besonders Schweizer Ärzte wie Paracelsus und Felix Plater (1530–1619) auf den Kretinismus hin, wobei Plater als erster auf das Vorkommen von Taubstummheit mit kropfiger und kretiner Degeneration hinwies. In seinem 1656 in Basel erschienen Buch „praxos medicae opus cum centuria posthuma, emendatum et auct. a Felice Platero" erwähnt er eine Art von Taubheit, die in den Alpengegenden auftritt und durch Taubstummheit in Verbindung mit einem Kropf charakterisiert ist. Ätiologisch nimmt Plater an, dass die Erkrankung durch eine „vom Kropf zum Ohr hin fliessende Flüssigkeit hervorgerufen wird". Er schreibt: Sicuti in alpinis regionibus, hac de causa multos difficilem auditum ab ortu, vel mox in aetatis progressu una cum strumis illis ob similem causam familiaribus habere cernimus (nach Politzer 1907).

Eingehende Untersuchungen zu diesem Problemkreis blieben Forschern im vorigen Jahrhundert vorbehalten – allen voran H. Bircher (1883), dessen Ausführungen zur endemischen Taubstummheit grundlegende Aspekte eröffnete. Die Untersuchungen wandten sich jetzt mikromorphologischen Methoden zu, was durch den weiteren Ausbau der Othistologie mit ihrer verfeinerten Technik wesentlich erleichtert wurde. Siebenmann (1906), Oppikofer (1913), Schlittler (1917), Brock (1920) und Nager (1921) stellten keine krankhaften Veränderungen des peripheren Hörorgans fest und hielten als Ursache für die Sprach- und Gehörstörungen eine zentrale Schädigung für wahrscheinlich. Andererseits bestand für die damaligen Autoren kein Zweifel, dass im peripheren Hörorgan beim voll ausgebildeten Krankheitsbild des endemischen Kretinismus typische morphologische Veränderungen nachweisbar sein können. Einmal Veränderungen im Mittelohr wie fehlende Pneumatisation des Warzenfortsatzes, mangelhaft angelegtes Antrum, Verengerung der Paukenhöhle, kleine Fensternischen, Verklumpungen von Gehörknöchelchen, Verdickung der Mittelohrschleimhaut, zum anderen Alterationen des Innenohres, die jedoch nur geringgradig ausgeprägt waren wie „atrophische Zustände der Hörzellen des Cortiorgans und der Ganglienzellen", auch Veränderungen der Stria vascularis (Alexander 1909, 1919), „eigentümliche Bildung des Cortiorgans (hyeline, säulenförmige Leiste) (Siebenmann 1904, Schlittler 1917, Nager 1917, Mayer 1919, Oppikofer 1921, Steurer 1922*a, b*).

Anlass zu vorliegender Studie war die Fülle von Publikationen mit mehr oder weniger wahrscheinlichen morphologischen Befunden am Hörorgan schilddrüsengestörter Patienten sowie der experimentell weitgehend ungeklärte Einfluss des Schilddrüsenhormons auf die Feinstrukturen des Innenohres. Die früheren Untersuchungen beschränkten sich fast ausschliesslich auf Beschreibungen von Krankheitsfällen des endemischen Kretinismus und der im späteren Lebensalter erworbenen Hypothyreose mit konsekutiver Hör-

2 Methodik

2.1 Versuchstiere, operative Massnahmen

Als Versuchstiere wurden 70 Meerschweinchen eines Inzuchtstammes im Gewicht von 250–350 g gewählt. Das Meerschweinchen erweist sich insofern als geeignetes Versuchstier, weil es besonders günstige Voraussetzungen für die *anatomische* Darstellung des Hörorgans mit Saccus endolymphaticus bietet. In Vollnarkose (intraperitoneal 0,015/100 g Körpergewicht Urethan oder Nembutal 0,004/100 g Körpergewicht) mit zusätzlicher lokaler 1%iger Novocain-Injektion wurde unter dem *Zeiss-Operationsmikroskop eine* vollständige *Thyreoidektomie durchgeführt.* Während der Vorversuche *zur* Erprobung der Operationstechnik der Thyreoidektomie verstarben einige Tiere am Operationstag, was auf eine zu lange Operationsdauer und eine zu starke Dehnung der *Halsweichteile mit Überstreckung* des Nervus vagus und Nervus sympathicus *zurückführen ist.* Die *meisten* Tiere vertrugen jedoch den Eingriff ohne wesentliche Komplikationen. Die Tötung der Tiere erfolgte nach 6–9 Wochen p. o. durch Dekapitation *in leichter Äthernarkose. Zur gleichen Zeit* wurden 10 Kontrolltiere getötet. Vor dem operativen Eingriff und *unmittelbar* vor der Tötung der Tiere wurde das Hörvermögen mittels des Preyer-Reflexes durch Händeklatschen in 1, 3 und 5 m Entfernung geprüft.

2.2 Präparatorische Arbeiten an der Cochlea und am Saccus endolymphaticus

Nach Entfernung der Schädelkalotte und Herauslösen des Gehirns wurde das Felsenbein eliminiert und die Bulla tympani – entsprechend der menschlichen Anatomie der Paukenhöhle – eröffnet. Um eine ausreichende Fixierung der Innenohrstrukturen zu erzielen, wurde der Stapes aus dem ovalen *Fenster herausgelöst, gleichzeitig* das runde *Fenster eröffnet.* Nur so wird eine optimale Zirkulation der *Fixierungslösung gewährleistet.* Zur Fixierung wurden eine Formalin-Calcium-Lösung nach Baker (1944) sowie das Greepsche Gemisch verwendet. Ausserdem wurden einige Schnecken zum Nachweis der Sulfhydryle mit Trichloressigsäure-Alkohol fixiert. Die rechte Schnecke, die jeweils *für die* Fermentuntersuchungen verwendet wurde, blieb für 3–6 Std. bei 4°C in dem Bakerschen Fixativ. Die linke Schnecke, die für die Untersuchungen des Mukopolysaccharidstoffwechsels vorgesehen war, fixierten wir im gleichen Gemisch über etwa 4 Std. Der Saccus endolymphaticus wurde *lediglich* für 2 Std. fixiert, da es sich hier nur um ein sehr kleines Gewebsstück handelt.

Nach der Fixierung wurde bei einem Teil der Schnecken die knöcherne Begrenzung des häutigen Labyrinthes unter dem Mikroskop *vollständig entfernt und* das Gewebsmaterial in Gelatine eingebettet. Bei dem anderen Teil wurde mit dem Bohrer der Knochen bis auf eine dünne Schicht abgefräst, danach erfolgte für ca. 3–5 Tage eine Entkalkung mit EDTA (Äthylen-Diamin-Tetra-Essigsäure). In besonderem Maße muss bei dieser Art der Entkalkung auf konstante Bedingungen geachtet werden: pH-Wert um 7,0, Temperatur 4°C und 1stündiger Wechsel der Entkalkungsflüssigkeit (Balogh und Nomura, *1964;* Nomura und Balogh, 1964*a, b;* Ishii und Balogh, *1966). Die linke Cochlea, die für die* Untersuchungen *zum* Mukopolysaccharidstoffwechsel vorgesehen war, wurde *nach der 24stündigen* Fixierung im Greep-Gemisch (Ameisensäure-Natrium-*Zitrat) entkalkt* (Greep et al. *1948)* und anschliessend in Paraffin eingebettet. *Die Paraffineinbettung* ist für den Nach-

störung. Experimentelle Untersuchungen der neueren Zeit stammen von Poulsen (1959), Ritter und Lawrence (1960), de Vos (1963), Ritter (1967).

Die eigenen Untersuchungen gehen vom thyreoidektomierten Meerschweinchen aus, quasi als Modell für die im späteren Lebensalter erworbenen Hypothyreosen und sollen die Frage beantworten, inwieweit mit Hilfe histochemischer Methoden etwaige durch den Tyroxinmangel hervorgerufene Veränderungen im Innenohr des Meerschweinchens nachweisbar werden und ob die Alterationen nähere Aufschlüsse über den Einfluss der Schilddrüsenhormone auf die Innenohrstrukturen ermöglichen. Von vornherein muss man sich darüber Rechenschaft geben, dass nur ein Abschnitt im komplexen Ablauf des Krankheitsbildes sichtbar wird und besonders elektrophysiologische Untersuchungen eine wertvolle Erweiterung der Experimente darstellen würden. Dennoch lassen die in jüngster Zeit verfeinerten Methoden histochemischer Innenohrexploration die Hoffnung zu, auch mit Hilfe der Morphologie Aussagen über eine mögliche Funktionsbeeinträchtigung machen zu können.

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weis von Mukopolysacchariden möglich da die zwischenzeitliche Behandlung der Schnitte mit Alkohol und Benzol – im Gegensatz zum Fermentnachweis – keinen Aktivitätsverlust nach sich zieht In ähnlicher Weise wurde mit dem Saccus endolymphaticus verfahren der rechte Saccus diente den Fermentuntersuchungen der linke wurde für den Mukopolysaccharidstoffwechsel vorgesehen wobei natürlich eine Entkalkung nicht erforderlich war

2.3 Spezielle fermenthistochemische Nachweisverfahren

2 3 1 *Unspezifische Esterasen*

Die unspezifische Esterase wurde nach Burstone (1957) mit Naphthol AS D-Azetat und Kupplung an Echtblausalz RR nachgewiesen Durch den Einfluss der Esterasen wird das Azetat abgespalten und der Naphtholrest freigesetzt Dieser Naphtholrest hat ein hohes Eiweissbindungsvermögen und heftet sich somit an Stellen der fermentativen Gewebsaktivität am Protein an Um den an Eiweiss gebundenen Naphtholrest sichtbar zu machen wird ein Diazoniumsalz angekuppelt (z. B Echtblausalz RR Echtgranatsalz GBC u a.) Dadurch wird eine Fermentaktivität in Form von Farbkörnchen sichtbar gemacht

Zur Kontrolle der Spezifität wird an einzelnen Schnitten entweder das Substrat oder das Diazoniumsalz weggelassen Die unspezifischen Esterasen und Cholinesterasen werden nach Barrnett und Seligman (1951) durch Gaben von 10 ³ M Natriumtaurocholat gehemmt Cholin und B Esterasen werden durch 10⁻⁸ M Diiso-Propylfluorophosphat die A Esterasen durch 10⁻⁴ M Natrium-Chloro-Mercuri-Benzoat gehemmt (Bergmann und Rimon 1958)

2 3 2 *β-Glukuronidase*

Die Darstellung der Glukuronidase erfolgt durch Inkubation der etwa 12 μ dicken Gelatineschnitte in der Substratlösung nach Seligman et al (1954) mit 6-Bromo-2 Naphthyl β-D-Glukuronid bei pH 4 9 und 37°C für 4–6 Std Danach wurde eine Postkupplung mit Echtblausalz RR und Echtgranatsalz GBC bei pH 7,5 vorgenommen Zur Kontrolle der Spezifität wurden Reaktionen mit alleiniger Echtblausalz-bzw Echtgranatsalzfärbung (ohne Substratinkubation) und alleiniger Substratinkubation (ohne Kupplung) durchgeführt Um eine Enzymdiffusion zu verhindern wurde der Substratlösung jeweils 1 M NaCl zugefügt (Schätzle und v Westernhagen 1966*b*)

2.3.3 *N Azetyl β-Glukosaminidase*

Die Glukosaminidase wurde in einem von Schätzle und v Westernhagen (1966*a*) leicht modifizierten Verfahren nach Pugh und Walker (1958 1961) durchgeführt Zum Nachweis wurde statt des Originalsubstrates Alpha Naphthyl Azetyl-β-Glukosamin das stabilere Naphthol AS LC N Azetyl β D Glukosamin verwendet Danach erfolgte Kupplung an ein Diazoniumsalz (Echtgranatsalz GBC) als Simultankupplung unter gleichen pH Bedingungen Einzelne Schnitte wurden auf ihre Fermentspezifität untersucht indem das Substrat fortgelassen oder aber mit Substrat eine über Wochen dauernde Formolfixierung durchgeführt wurde welche das Ferment inaktiviert

2.3 4 *β-Galaktosidase*

Hierbei wurde die Methode von Rutenburg et al (1958) angewandt 12 μ dicke Gefrierschnitte wurden für 3–12 Std in einer Lösung von 6-Bromo-2 Naphthyl β-D-Galaktosid bei pH 4 95 und 37°C Temperatur inkubiert Die anschliessende Kupplung erfolgte mit Echtgranatsalz GBC Danach wurde bei pH 7 4 und Zimmertemperatur 10–15 Min nachgekuppelt.

Daneben wurden auch Schnitte mit Naphthol AS LC β-D-Galaktosid als Substrat (1? Std bei pH 4,95 und 37°C Temperatur) in Verbindung mit Echtgranatsalz GBC Postkupplung (10 Min pH 7 4 Raumtemperatur) behandelt

Die Kontrollreaktionen wurden an inkubier

ten Schnitten ohne Diazokupplung sowie an nicht substratinkubierten Schnitten durchgeführt.

3.5 Aryl Sulfatase

Gefrierschnitte von 12 β Dicke wurden für 4–6 Std bei 37°C und pH 6.1 in einer Lösung von Kalium-6-Benzoyl-2-Naphthylsulfat nach Rutenburg und Seligman (1956) inkubiert. Wie in der Originalmethode beschrieben, wurde Kochsalz zugesetzt. Nach kurzer Wasserung erfolgte die Postkupplung mit Echtgranatsalz GBC oder Echtrotsalz TR bei pH 7.6 (ca. 10 Min.) bei Raumtemperatur.

Kontrollreaktionen wurden unter Weglassung des Substrates sowie mit alleiniger Inkubation ohne nachfolgende Kupplung ausgeführt.

2.4 Nachweis der Sulfhydryle und Gesamtsulfhydryle

Die für die Untersuchung von Sulfhydrylen vorgesehenen Schnecken wurden mit Trichloressigsäure Alkohol fixiert, anschliessend erfolgte eine kurzdauernde Entkalkung mit EDTA. Die 10 μ dicken Paraffinschnitte wurden wie folgt bearbeitet:

4.1 Sulfhydrylnachweis nach Barrnett und Seligman (1952, 1954)

mit dem DDD-Reagens bei pH 8.5 mit Veronal-Azetat-Puffer und Kupplung an Echtgranatsalz GBC bei pH 7.4 mit Phosphatpuffer. Durch die Verwendung von Echtgranatsalz entsteht eine Rotfärbung. Die Kontrollreaktion erfolgte durch Blockierung der freien SH-Gruppen mittels eines Zusatzes von Monojodessigsäure (0.1 M); die „tragen" SH-Gruppen wurden mittels Sublimat blockiert.

4 Gleichzeitiger Nachweis von Sulfhydrylen und Disulfiden (Gesamtsulfhydryle)

Es erfolgte eine Überführung der SS-Gruppen in SH-Gruppen durch Thioglykolsäure (0.5 M bei 37°C und pH 8.0), danach Nachweis der Gesamtsulfhydryle mit der DDD-Methode.

2.5 Histochemischer Nachweis von Gluko-Mukoproteiden, sauren Mukopolysacchariden

2.5.1 PAS-Reaktion nach McManus (1946) Hotchkiss (1948)

Nach Formalinfixierung und Entkalkung erfolgt die Paraffineinbettung.

_5._ PAS Alcianblau nach Runge, Ebner und Lindenschmidt (1956)

Als Kontrollreaktion wurde eine Methylierung des Schnittes durchgeführt, was sich infolge Blockierung saurer Substanzen in einer verringerten Anfärbbarkeit dokumentiert (Fraenkel-Conrat und Olcott, 1945; Fisher und Lillie 1954). Ausserdem wendeten wir die Sulfatierung nach Kramer und Windrum (1954) an. Mit dieser Methode lassen sich zusätzliche Sulfatgruppen auf ein entsprechendes Substrat übertragen. Durch die Zunahme der Sulfatgruppen resultiert eine stärkere Metachromasie-Reaktion.

Die Reaktionen 1 und wurden ergänzt durch die Anwendung von Amylase, Ribonuklease und Hyaluronidase, um die den angeführten Fermenten entsprechenden Substrate aus dem Schnitt zu entfernen.

2.5.3 Eisenbindungsreaktion nach Hale (1946)

Eisenbindungsreaktion in der Modifikation nach *Graumann und Clauss (1958)* oder *Hale* PAS-Reaktion nach Ritter und Oleson (1950).

5.4 Metachromasie-Reaktionen

5.4.1 Azur A 0,2%ig bei verschiedenen pH-Werten (1.5, 3.5, 4.5) mit Walpole Puffer an Paraffinschnitten (Walpole 1914). Es erfolgten die gleichen Kontrollreaktionen wie unter PAS-Alcianblaufärbung oben angeführt. Vor der Reaktion wurden die Schnitte mit Ribonuklease behandelt, um Nukleinsäure herauszulösen. Weitere Kontrollreaktionen erfolgten mit Hyaluronidase, um die hyaluronidasesensiblen MPS zu entfernen.

weis von Mukopolysacchariden möglich da die zwischenzeitliche Behandlung der Schnitte mit Alkohol und Benzol – im Gegensatz zum Fermentnachweis – keinen Aktivitätsverlust nach sich zieht In ähnlicher Weise wurde mit dem Saccus endolymphaticus verfahren der rechte Saccus diente den Fermentuntersuchungen der linke wurde für den Mukopolysaccharidstoffwechsel vorgesehen wobei natürlich eine Entkalkung nicht erforderlich war

2.3 Spezielle fermenthistochemische Nachweisverfahren

2 3 1 *Unspezifische Esterasen*

Die unspezifische Esterase wurde nach Burstone (1957) mit Naphthol AS-D-Azetat und Kupplung an Echtblausalz RR nachgewiesen Durch den Einfluss der Esterasen wird das Azetat abgespalten und der Naphtholrest freigesetzt Dieser Naphtholrest hat ein hohes Eiweissbindungsvermögen und heftet sich somit an Stellen der fermentativen Gewebsaktivität am Protein an Um den an Eiweiss gebundenen Naphtholrest sichtbar zu machen wird ein Diazoniumsalz angekuppelt (z B Echtblausalz RR Echtgranatsalz GBC u a) Dadurch wird eine Fermentaktivität in Form von Farbkörnchen sichtbar gemacht

Zur Kontrolle der Spezifität wird an einzelnen Schnitten entweder das Substrat oder das Diazoniumsalz weggelassen Die unspezifischen Esterasen und Cholinesterasen werden nach Barrnett und Seligman (1951) durch Gaben von 10 ³ M Natriumtaurocholat gehemmt Cholin und B Esterasen werden durch 10 ⁸ M Diiso-Propylfluorophosphat die A Esterasen durch 10 ⁴ M Natrium-Chloro-Mercuri Benzoat gehemmt (Bergmann und Rimon 1958)

2 3 2 *β-Glukuronidase*

Die Darstellung der Glukuronidase erfolgt durch Inkubation der etwa 12 μ dicken Gelatineschnitte in der Substratlösung nach Seligman et al (1954) mit 6-Bromo-2 Naphthyl β-D-Glukuronid bei pH 4 9 und 37°C für 4–6 Std Danach wurde eine Postkupplung mit Echtblausalz RR und Echtgranatsalz GBC bei pH 7,5 vorgenommen Zur Kontrolle der Spezifität wurden Reaktionen mit alleiniger Echtblausalz-bzw Echtgranatsalzfärbung (ohne Substratinkubation) und alleiniger Substratinkubation (ohne Kupplung) durchgeführt. Um eine Enzymdiffusion zu verhindern wurde der Substratlösung jeweils 1 M NaCl zugefügt (Schätzle und v Westernhagen 1966*b*)

2 3.3 *N A etyl β-Glukosaminidase*

Die Glukosaminidase wurde in einem von Schätzle und v Westernhagen (1966*a*) leicht modifizierten Verfahren nach Pugh und Walker (1958 1961) durchgeführt Zum Nachweis wurde statt des Originalsubstrates Alpha Naphthyl-Azetyl β-Glukosamin das stabilere Naphthol AS LC N Azetyl β D Glukosamin verwendet Danach erfolgte Kupplung an ein Diazoniumsalz (Echtgranatsalz GBC) als Simultankupplung unter gleichen pH Bedingungen Einzelne Schnitte wurden auf ihre Fermentspezifität untersucht indem das Substrat fortgelassen oder aber mit Substrat eine über Wochen dauernde Formolfixierung durchgeführt wurde welche das Ferment inaktiviert.

2 3 4 *β-Galaktosidase*

Hierbei wurde die Methode von Rutenburg et al (1958) angewandt 12 μ dicke Gefrierschnitte wurden für 3–12 Std in einer Lösung von 6-Bromo-2 Naphthyl β-D-Galaktosid bei pH 4 95 und 37°C Temperatur inkubiert Die anschliessende Kupplung erfolgte mit Echtgranatsalz GBC Danach wurde bei pH 7 4 und Zimmertemperatur 10–15 Min nachgekuppelt

Daneben wurden auch Schnitte mit Naphthol AS-LC β-D-Galaktosid als Substrat (1? Std bei pH 4 95 und 37°C Temperatur) in Verbindung mit Echtgranatsalz GBC Postkupplung (10 Min pH 7 4 Raumtemperatur) behandelt

Die Kontrollreaktionen wurden an inkubier

Schnitten ohne Diazokupplung sowie an ht substratinkubierten Schnitten durchgeführt.

2.3.5 Aryl Sulfatase

Gefrierschnitte von 12 µ Dicke wurden für 6 Std bei 37°C und pH 6.1 in einer Lösung aus Kalium-6-Benzoyl-2-Naphthylsulfat nach Rutenburg und Seligman (1956) inkubiert. Wie in der Originalmethode beschrieben, wurde Kochsalz zugesetzt. Nach kurzer Wässerung folgte die Postkupplung mit Echtgranatsalz GBC oder Echtrotsalz TR bei pH 7.6 (ca. 10 Min.) bei Raumtemperatur.

Kontrollreaktionen wurden unter Weglassung des Substrates sowie mit alleiniger Inkubation ohne nachfolgende Kupplung ausgeführt.

2.4 Nachweis der Sulfhydryle und Gesamtsulfhydryle

Die für die Untersuchung von Sulfhydrylen vorgesehenen Schnecken wurden mit Trichloressigsäure-Alkohol fixiert, anschliessend erfolgte eine kurzdauernde Entkalkung mit EDTA. Die 10 µ dicken Paraffinschnitte wurden wie folgt bearbeitet:

2.4.1 Sulfhydrylnachweis nach Barrnett und Seligman (195 1954)

mit dem DDD-Reagens bei pH 8.5 mit Veronal-Azetat-Puffer und Kupplung an Echtgranatsalz GBC bei pH 7.4 mit Phosphatpuffer. Durch die Verwendung von Echtgranatsalz entsteht eine Rotfärbung. Die Kontrollreaktion erfolgte durch Blockierung der freien SH-Gruppen mittels eines Zusatzes von Monojodessigsäure (0.1 M); die „maskierten" SH-Gruppen wurden mittels Sublimat blockiert.

2.4.2 Gleichzeitiger Nachweis von Sulfhydrylen und Disulfiden (Gesamtsulfhydryle)

Es erfolgte eine Überführung der SS-Gruppen in SH-Gruppen durch Thioglykolsäure (0.5 M bei 37°C und pH 8.0), danach Nachweis der Gesamtsulfhydryle mit der DDD-Methode.

2.5 Histochemischer Nachweis von Gluko-Mukoproteiden, sauren Mukopolysacchariden

2.5.1 PAS-Reaktion nach McManus (1946) Hotchkiss (1948)

Nach Formalinfixierung und Entkalkung erfolgt die Paraffineinbettung.

2.5.2. PAS-Alcianblau nach Runge, Ebner und Lindenschmidt (1956)

Als Kontrollreaktion wurde eine Methylierung des Schnittes durchgeführt, was sich infolge Blockierung saurer Substanzen in einer verringerten Anfärbbarkeit dokumentiert (Fraenkel-Conrat und Olcott, 1945; Fisher und Lillie 1954). Ausserdem wendeten wir die Sulfatierung nach Kramer und Windrum (1954) an. Mit dieser Methode lassen sich zusätzliche Sulfatgruppen auf ein entsprechendes Substrat übertragen. Durch die Zunahme der Sulfatgruppen resultiert eine stärkere Metachromasie-Reaktion.

Die Reaktionen 1 und 2 wurden ergänzt durch die Anwendung von Amylase, Ribonuklease und Hyaluronidase, um die den angeführten Fermenten entsprechenden Substrate aus dem Schnitt zu entfernen.

2.5.3 Eisenbindungsreaktion nach Hale (1946)

Eisenbindungsreaktion in der Modifikation nach Graumann und Clauss (1958) oder Hale-PAS-Reaktion nach Ritter und Oleson (1950).

2.5.4 Metachromasie-Reaktionen

2.5.4.1 Azur A 0.2% bei verschiedenen pH-Werten (1.5, 3.5, 4.5) mit Walpole-Puffer an Paraffinschnitten (Walpole 1914). Es erfolgten die gleichen Kontrollreaktionen wie unter „PAS-Alcianblaufärbung" oben angeführt. Vor der Reaktion wurden die Schnitte mit Ribonuklease behandelt, um Nukleinsäure beseitigen. Weitere Kontrollreaktionen erfolgten mit Hyaluronidase, um die hyaluronidasesensiblen MPS zu entfernen.

3 Experimentelle Untersuchungsergebnisse – Kontrolltiere (Meerschweinchen)

3.1 Normale fermenthistochemische Befunde der Cochlea

3.1.1 *Unspezifische Esterase*

Die Esterasereaktion fällt intensiv positiv an den Deiters- und Hensenzellen aus, also in *den dem Stützzellensystem zuzuordnenden* Zellen. Die Sinneszellen reagieren deutlich geringer, von ihnen haben die inneren Haarzellen im Vergleich zu den äusseren eine relativ kräftigere Blaufärbung. Die Basilarmembran ist negativ, positiv die sog. tympanale Belegschicht sowie die Stria vascularis. Sulcus spiralis externus und internus sind in ihrem epithelialen Bereich kräftig positiv.

3.1.2 *β-Glukuronidase*

Eine mässige bis starke Reaktion zeichnet sich im Bereich des N. acusticus ab, während das Cortiorgan wesentlich schwächer positiv war. In allen anderen Abschnitten des Ductus cochlearis sieht man bei der Kupplung an Echtgranatsalz GBC geringfügige bis schwach granatrote Granula. Besonders in der apikalen und perinukleären Zone der inneren und äusseren Haarzellen. Die Basilarmembran ist negativ, es findet sich eine mässige Rotfärbung der tympanalen Belegschicht. Auffällig ist eine stärkere Reaktion in der Reissnerschen Membran, die sich in etwas geringfügigerer Intensität auch in der Stria vascularis wiederholt.

3.1.3 *N-Acetyl-β-Glukosaminidase*

Der auffallendste Befund ist die intensive Enzymreaktion der äusseren Haarzellen und hier besonders in der apikalen Zone. Die inneren Haarzellen dagegen zeigen eine schwächere Fermentaktivität. Die Zellen des Sulcus spiralis *besitzen eine schwächere Fermentaktivität.* Die Zellen des Sulcus spiralis externus zeigen insgesamt nur eine schwache Reaktion. Kräftig dagegen reagiert die Stria vascularis.

3.1.4 *β-D-Galaktosidase*

Die Fasern des N. acusticus sowie die vom Cortiorgan zum Ganglion *cochleae ziehenden* Fasern weisen eine sehr deutliche Fermentaktivität auf. Ebenso werden reichlich Fermentgranula im Ganglion spirale nachweisbar, während das Cortiorgan vergleichsweise schwach oder fast gar nicht reagiert. Im Plexus cochlearis in der Nähe des N. acusticus zeichnet sich eine stärkere Fermentaktivität ab. Zahlreiche Fermentgranula finden sich zudem in der Stria vascularis zwischen den Pigmentanhäufungen.

3.1.5 *Aryl-Sulfatase*

Es zeigt sich eine intensive Reaktion in den Fasern des N. acusticus sowie in den prägangliönären Fasern. Auch die Haarzellen reagieren deutlich positiv, wobei die Farbkörnchen überwiegend perinukleär zu finden sind. Die Stria vascularis verhält sich in ihrer Fermentaktivität kräftig positiv (Tab. 1).

3.2. Normale fermenthistochemische Befunde des Saccus endolymphaticus

Die unspezifischen Esterasen finden sich in mittelstarker Reaktion im Epithel der Pars intermedia des S. e., die Pars distalis reagiert wesentlich schwächer. Von den sog. freien Zellen im Saccuslumen weisen einige Zellen eine erhebliche Ferm*entaktivität auf, während* sich andere praktisch negativ ausweisen.

Die Glukosaminidase-Reaktion verhält sich in der Lokalisation des Fermentes sehr ähnlich dem Esterase-Nachweis, wenn auch die

Tabelle I *Fermenthistochemische Aktivitäten an der Cochlea des Kontrolltiers (Meerschweinchen)*

	Esterase	Glukuronidase	Glukosaminidase	Sulfatase	Galaktosidase
Stria vasc.	+	++	+	++	++
Sulc. spir. ext.	+	+0	+0	+0	+0
Lig. spirale	0	+0	0	+0	+0
Gangl. spirale	0	+	++	+0	++
Äussere HZ	+0	+0	++	+	+0
Innere HZ	+	+	+0	+	+0
Deiters Zellen	++	0	+0	+0	+0
Hensen Zellen	++	+0	+0	0	+0
Pfeiler Zellen	+0	0	0	0	0
Memb. tect.	0	0	0	0	0
Reissner M.	+0	+	+0	0	+0
Basil. M.	0	0	0	0	0
Tymp. Belegsch.	+	0	0	0	+0
Limb. spirale		+0	0	+0	+
N. acusticus	0	+	0	++	++
Präganglionäre F.	0	+	0	++	++
Plex. cochlearis	+0	+0	+	+0	+0

Enzymaktivität vergleichsweise starker ausfällt. Es besteht eine starke Ansammlung von Fermentgranula in der Pars intermedia (Epithel). Ausserdem weisen zahlreiche intrasacculäre Zellen einen hohen Fermentgehalt auf.

Der Nachweis der Glukuronidase und Galaktosidase stimmt weitgehend mit den Ergebnissen von der Esterase und der Glukosaminidase überein, wenn auch insgesamt die Fermentreaktionen etwas schwächer ausfallen.

Die Sulfatase lässt besonders in der Pars intermedia (Epithel) eine sehr starke Fermentaktivität erkennen, die sich auch in den sog. freien Zellen abzeichnet (Tab. II).

3.3 Normale Verteilung von Sulfhydrylen (SH) und Gesamtsulfhydrylen (SS+SH) in der Cochlea

Die Stria vascularis reagiert intensiv positiv (SH-Reaktion), ebenfalls die Pfeilerzellen. Positiv verhalten sich auch die Zellen des Ganglion spirale und die Nervenfasern des N. acusticus. Äussere und innere Haarzellen weisen einen deutlichen, wenn auch nicht hohen SH-Gehalt auf. Mit der Methode nach Barrnett und Seligman lassen sich auch noch positive Bereiche im Limbus spiralis, Lig. spirale und Reissner Membran erfassen. Erwartungsgemäss fallen beim Gesamtsulfhydryl-

Tabelle II *Fermenthistochemische Aktivitäten am Saccus endolymphaticus des Kontrolltiers (Meerschweinchen)*

	Esterase	Glukuronidase	Glukosaminidase	Sulfatase	Galaktosidase
Epithelien Pars intermedia			+		+
Epithelien Pars distalis	+0	+0	+0		0
Bindegewebe	0	0	0	+0	+0
Zellen im Bdg.	0	0		+0	+0
Sog. freie Zellen	+0–	0–+	0–+	–++	+0–+

nachweis (SS- +SH-Gruppen) die Reaktionen noch stärker aus – in der Stria vascularis jedoch relativ geringer als im Lig. spirale oder in den Pfeilerzellen Die SH-Gruppen zeigen an Orten vermehrter Stoffwechseltätigkeit ein Überwiegen z B in der Stria vascularis während die SS-Gruppen (Disulfide) mehr an den Orten vorkommen denen eine Stützfunktion zugeordnet wird (Pfeilerzellen Basilarmembran) (Müsebeck und Schätzle 1963)

3 4 Normale histochemische Befunde von Gluko-Mukoproteiden sauren Mukopolysacchariden in der Cochlea

3 4 1 *PAS Alcianblau-Reaktion (nach Runge Ebner und Lindenschmidt (1956)*

Es findet sich bei der PAS-Alcianblaufärbung eine intensive Reaktion im Bereiche der Basilarmembran sowie den Fasern des Verankerungssystems im Lig spirale und Limbus spiralis Das Cortiorgan und die tympanale Belegschicht sind praktisch frei Auffallend ist eine stärker blau gefärbte Zone im Bereiche des Ansatzes der Basilarmembran im Lig spirale In der Stria vascularis ist kaum eine Farbreaktion zu erkennen Eine sehr starke Anfärbung zeigt die Tectorialmembran

Durch eine zusätzliche Methylierung werden die sauren Gruppen blockiert was sich im Ausbleiben der Anfärbbarkeit mit Alcianblau zeigt Überträgt man zusätzliche Sulfatgruppen so resultiert daraus keine stärkere Anfärbbarkeit mit Alcianblau Nach Hyaluronidasebehandlung der Schnitte nimmt der Farbton im Bereich der Membrana basilaris und der Membrana tectoria leicht ab

3 4 2 *Eisenbindungsreaktion (nach Hale 1946 modifiziert nach Graumann und Clauss 1958) oder PAS Hale Reaktion (nach Ritter und Oleson 1950)*

Im grossen und ganzen werden ähnliche Farbreaktionen wie bei der PAS-Alcianblaufärbung beobachtet Intensiv reagieren Membrana tectoria und Basilarmembran stark blau gefärbt ist auch die Stria vascularis Die Membrana tectoria weist eine dunkelblaue Farbe auf Auch das bindegewebige zellarme Dreieck am Ansatzpunkt der Basilarmembran am Lig. spirale wird stark angefärbt

Die Kontrollreaktionen ähneln weitgehend den Ergebnissen bei der PAS Alcianblaufärbung unter Anwendung von Methylierung und Sulfatierung.

3 4 3 *Metachromasie Reaktionen*

3 4 3 1 *Azur A* Bei pH 4,5 ergeben sich kräftige metachromatische Reaktionen im Bereiche der Basilarmembran des Knochen Bindegewebes am Modiolus sowie des perivasculären Bindegewebes Eine geringere Metachromasie zeigt sich im Lig. spirale und im bindegewebigen Dreieck an der Ansatzstelle der Basilarmembran am Lig. spirale. Die Stria vascularis verhält sich negativ Eine überaus intensive Metachromotropie weist die Membrana tectoria aus.

Bei pH 3 finden sich Metachromasie Reaktionen in der Basilarmembran und deren Verankerungssystem sehr kräftige Reaktion der Tectorialmembran Stria vascularis und Cortiorgan verhalten sich orthochromatisch

Bei pH 1,5 zeigt sich lediglich eine orthochromatische Reaktion im Bereich der Cochlea

3 4 3 2 *Toluidinblau mit abgestuften $CaCl_2$-Konzentrationen* Bei 0 04 M Lösung des basischen Farbstoffes färben sich nur Stria vascularis und Cortiorgan orthochromatisch an Darüberhinaus lässt sich eine diffuse Rotfärbung an vielen Cochleastrukturen feststellen die zum grössten Teil unspezifisch sein dürfte Ganz ähnliche Verhältnisse finden sich bei 0 1 M Lösungskonzentrationen Erst bei 0 2 M Lösung tritt eine kräftige Metachromasie in der Basilarmembran der Membrana tectoria geringeren Grades auch im Lig spirale und Limbus spiralis auf Die Ergebnisse sind weitgehend vergleichbar mit den Reaktionen von Azur A bei pH 3,5 Bei der 0 4

Tabelle III *Verteilung und Reaktionsintensität der Gluko-Mukoproteide sowie saure Mukosubstanzen in der Cochlea des Kontrolltieres*

	Gluko-Mukoproteide Saure Mukosubstanzen PAS-Alcianblau	Saure Mukosubstanzen Azur A				Saure Mukosubstanzen Toluidinblau			Gluko-Mukoproteide Saure Mukosubstanzen Eisenbindungsreaktion
		pH 1,5	pH 3,0	pH 4,5		0,4 m	0,– m	0,04 m	
Stria vasc	0		orth.	orth.		0	●		–+
Sulc. spir. ext	0		(0)						
Lig. spirale	+0		orth.	0		+	+●		+0
Os. spirale	+0		++			++	+–		0
Äußere HZ	0	Orthochromatisch	0	0	Orthochromatisch	0	0		0
Innere HZ	0		●	0		0	0		0
Deiters Zellen	●		0	0		0	0		0
Hensen Zellen	0		0	0		●	0		0
Pfeiler Zellen	0		●	0		0	0		0
Memb. tect.			+	+		+	+		
Reissner M.	●			0		0	0		0
Basal M.			+	++					
Tymp. Belegsch.	0			0		●	●		0
Limb. spiralis	0		0	++		+0	+		+
N. acusticus	0								
Prim.ganglionära F.	0								
Endolymph.-Raum	●		0	0		0	0		0
Perilymph.-Raum	0		0	0		●	0		0
Gefäß-Bdg. Modiolus						++	+		
Knochengrundsubst.									+

* Größtenteils unspezifische Rötung

M-Lösung sieht man nur orthochromatische Effekte (Tab. III).

3.5 Gluko-Mukoproteide, saure Mukopolysaccharide im Saccus endolymphaticus

Bei der PAS-Alcianblaufärbung reagiert das Bindegewebe der Pars intermedia stärker positiv, die Epithelien der Pars intermedia und der Pars distalis sind nur schwach angefärbt oder verhalten sich negativ. Der Inhalt der Sacculichtung, der sich mit Hämatoxilin-Eosin schwach rosa anfärbt, lässt bei der PAS-Alcianblaufärbung kaum eine Reaktion erkennen. Die sog. freien Zellen im Saccuslumen sind zumeist nicht angefärbt. Bei den Metachromasiemethoden, die an einzelnen Sacci endolymphatici angestellt wurden, fand sich bei Azur A pH 4,5 eine Metachromasie im Bindegewebe der Pars intermedia und distalis. Entsprechend fielen die Ergebnisse der Toluidinblau-Färbung aus. Wegen des nur sehr geringen Gewebsmaterials, welches man bei Entnahme des endolymphatischen Sackes gewinnt, konnten jeweils nicht alle Reaktionen an einem Gewebsstück durchgeführt werden.

4 Experimentelle Untersuchungsergebnisse – thyreoidektomierte Tiere (Meerschweinchen)

4.1 Allgemeines Verhalten der Tiere

8–14 Tage nach der durchgeführten Thyreoidektomie zeigten fast alle Versuchstiere eine deutliche Abnahme der motorischen Aktivität, die Fresslust liess nach, einige Tiere sassen teilnahmslos im Käfig, andere reagierten auffällig aggressiv auf taktile Reize. 9 Tiere liessen nach 6–7 Wochen eine erhebliche Schwerhörigkeit erkennen, was mit Hilfe des Auslösens des Preyer-Reflexes ermittelt werden konnte. Etwa die Hälfte der anderen Tiere zeigten ein herabgesetztes Hörvermögen verschiedener gradueller Abstufung (Auslösen des Preyer-Reflexes in 1–3 m).

4.2 Makroskopische Veränderungen im Bereich der Bulla tympani nach Thyreoidektomie

Von den 9 stark schwerhörigen Tieren war bei 3 Meerschweinchen in der eröffneten Bulla tympani eine verdickte, glasig aussehende Schleimhaut zu erkennen, was als mögliche myxomatöse Veränderung der Mittelohr... sehr schwer isolierbar werden. Die myxomatöse Schleimhaut umgibt auch weitgehend das ovale Fenster mit der Stapesnische. Bei 6 der 9 Tiere war es zu einer eitrigen Mittelohrentzündung gekommen, ein Befund, der beim Meerschweinchen schon unter normalen Bedingungen gar nicht so selten ist, im vorliegenden Fall jedoch durch den Hormonmangel begünstigt sein könnte.

4.3 Fermenthistochemische Befunde der Cochlea

4.3.1 *Unspezifische Esterase*

Vergleicht man Abb. 1 (Kontrolltier) mit Abb. 2 (Versuchstier), so lässt sich unschwer die verminderte Fermentaktivität beim Hypothyreosetier feststellen. Das Kontrolltier zeigt eine Reaktion des Fermentes im Bereiche der inneren und äusseren Haarzellen, eine stärkere in den Deiters- und Hensenzellen. Auch in der tympanalen Belegschicht finden sich zahlreiche Farbkörnchen. Die Fermentgranula sind beim Normaltier besonders am apikalen Zellpol der inneren und äusseren Haarzellen lokalisiert.

6 Wochen nach der erfolgten Thyreoidektomie nimmt die Esterase bei fast allen Tieren deutlich ab. Diese Tatsache wird besonders auffällig im Bereich der Sinnes- und Stützzellen (Deiterszellen, Hensenzellen sowie Pfeilerzellen). Auch die recht kräftige Reaktion des Fermentes in der Stria vascularis fällt bei den Versuchstieren ab. Die tympanale Belegschicht an der Lamina basilaris ist praktisch frei von Fermentgranula. In der Reissner-Membran ist gleichfalls eine verminderte Fermentaktivität nachweisbar. Die durchgeführten Spezifitätskontrollen liessen den Schluss zu, dass es sich bei den Farbreaktionen um den Ausdruck der Esteraseaktivität handelt.

4.3.2 *β-Glukuronidase*

Beim Kontrolltier fällt die Glukuronidase-Reaktion besonders kräftig in der Stria vascularis, im N. acusticus und dessen präganglionären Fasern aus. Auch die Reissner-Membran weist eine stärkere Fermentaktivität auf, während die Sinneszellen relativ schwach reagieren. Auf der Übersichtsaufnahme sieht man besonders eindrucksvoll die dunkel gefärbte Stria vascularis sowie die zahlreichen Farbgranula in den präganglionären Fasern des N. acusticus und im Bereiche des Ganglion spirale. Auch die Reissner-Membran zeichnet sich durch eine dunklere Farbe ab. Beim Versuchstier nimmt die Glukuronidase-Aktivität

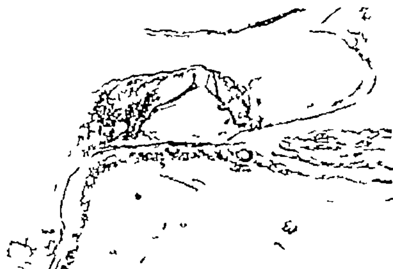


Abb 1 Nachweis der unspezifischen Esterase in der Cochlea (Kontrolltier). 590-fache Vergr

insgesamt weniger oder gar nicht ab als dies beim Esterasenachweis beobachtet werden konnte Am ehesten lasst sich in den inneren Haarzellen eine gewisse Reduzierung der Enzymaktivität belegen

Man sieht eine Anhaufung von Fermentgranula im Bindegewebe des Sulcus spiralis externus (Prominentia spiralis) einem Ort dem eine spater noch zu erorternde Bedeutung zukommen dürfte Ganz unverandert bleibt die kräftige Glukuronidase Reaktion im N acusticus und in den präganglionären Fasern.

Kontrollreaktionen auf die Spezifität des Enzymnachweises liessen den Schluss zu dass hier die Aktivität der Glukuronidase nachgewiesen wurde

4.3.3 *N Acetyl-β-Glukosaminidase*

Beim Normaltier findet sich eine hohe Glukosaminidase Aktivität im apikalen Anteil des



Abb. 2 Nachweis der unspezifischen Esterase in der Cochlea (Versuchstier). 590-fache Vergr



Abb 3 Nachweis der Glukosaminidase in der Stria vascularis (Kontrolltier). 590-fache Vergr

und nicht signifikante Unterschiede gegenüber den Kontrolltieren eruieren

4 3 4 *β-Galaktosidase*

Die Galaktosidase-Reaktion ist besonders stark in den Fasern des N acusticus und den vom Cortiorgan zum Ganglion spirale ziehenden Nervenfasern Im Ganglion spirale selbst ist die Reaktion überwiegend im perizellulären Bindegewebe nachzuweisen während das Zytoplasma nur einzelne Fermentgranula enthält Beim Kontrolltier erkennt man das spärlich fermentpositive Cortiorgan und die kräftiger reagierenden Nervenfasern des präganglionären Anteils des N acusticus Fast identisch sind die Fermentreaktionen beim Versuchstier Es tritt danach keine signifikante Reduzierung der Fermente mehr ein

Neben den beschriebenen Prädilektionsstel

Zytoplasmas der äusseren Haarzellen In der Stria vascularis (Abb 3) und im Zytoplasma der Ganglienzellen des Ganglion spirale Die Pfeilerzellen sind fast negativ einige Fermentkörnchen lassen sich in den Deiters- und Hensenzellen nachweisen Auch im Bereich der Prominentia spiralis ist eine deutliche Fermentaktivität festzustellen Die Membrana tectoria ist völlig frei

Im Vergleich dazu lassen die thyreoidektomierten Tiere eine Abnahme der Fermentaktivität erkennen Sie betrifft die äusseren Haarzellen die Stria vascularis (Abb 4) und die Zellen des Ganglion spirale Ziemlich unverändert bleibt der Fermentgehalt der Prominentia spiralis An den Orten die ohnehin nur eine geringe Farbreaktion im Sinne des Enzymnachweises zeigen lassen sich auch unter Versuchsbedingungen nur unwesentliche



Abb 4 Nachweis der Glukosaminidase in der Stria vascularis (Versuchstier). 590-fache Vergr

Tabelle IV *Fermentaktivitäten in verschiedenen Abschnitten der Cochlea des thyreoidektomierten Meerschweinchens*

	Esterase	Glukuronidase	Glukosaminidase	Sulfatase	Galaktosidase
Stria vasc.	+0	+	+	+	
Sulc spir ext.	+0	+0	0	+0	+0
Lig spirale	0	+0	0	0	0
Ggl spirale	0	+	+	+0	
Äußere HZ	0	+0	0		+0
Innere HZ	0	0	0		0
Deiters Zellen		+0	0	+0	0
Hensen Zellen	+	0	+0	+0	0
Pfeiler Zellen	+0	0	0	+0	+0
Memb tect	0	0	0	0	0
Reissner M	0	+0	+●	+0	0
Basal M	+0	0	0	0	0
Tymp Belegsch	0	0	0	0	+0
Limb. spiralis	0	+0	0	+0	
N acusticus	●	+	●		+
Praeganglionäre F	0	++	●		
Plex cochlearis	●	+0	+	0	+0

len der Galaktosidase-Aktivität lässt diese sich darüberhinaus auch in der Stria vascularis, in der Reissner Membran, im Epithel des Limbus spiralis internus und externus, nicht aber in der Membrana *tectoria* nachweisen. (Tab. IV.)



Abb. 5 Nachweis der Sulfatase in der Stria vascularis (Kontrolltier) 900-fache Vergr.

4.3.5 *Aryl-Sulfatase*

Die Sulfatase Reaktion fällt besonders stark in den Nervenfasern des N. acusticus (präganglionären Fasern) auf. Die Zellen des Ganglion spirale enthalten im Zytoplasma nur wenige Fermentgranula. Ausserdem erkennt man neben den positiven präganglionären Nervenfasern auch die deutliche Enzymaktivität in den inneren und äusseren Haarzellen, wobei die äusseren HZ intensiver reagieren. Auch die Stria vascularis weist zahlreiche Fermentgranula auf, die aus der Abb. 5 hervorgehen.

Die Membrana tectoria lässt keinerlei Fermentaktivität erkennen. Vergleicht man hierzu die histochemischen Reaktionen der unter Versuchsbedingungen stehenden Tiere, so kann man mit geringen Einschränkungen feststellen, dass die Enzymaktivitäten unverändert sind, besonders kräftige Reaktion in den Nervenfasern in der Stria vascularis.

Die Einschätzung der Fermentaktivitäten in der Cochlea des thyreoidektomierten Meerschweinchens lassen sich nach Tab. IV vornehmen.



Abb. 6. Nachweis der unspez. Esterase im Saccus endolymphaticus (Kontrolltier). 480-fache Vergr.

4.4 Nachweis der Sulfhydryle und Gesamtsulfhydryle (SH+SS) in der Cochlea

Beim Normaltier findet sich eine kräftige SH-Reaktion in den inneren und äusseren Haarzellen, in geringerem Ausmasse in den Pfeilerzellen sowie den Hensen- und Deiterszellen. Vergleiche mit der Reaktion der Gesamtsulfhydryle zeigen, dass die Farbintensität in der Stria vascularis relativ geringfügiger zunimmt als in den Zellen des sog. Stützsystems. Das Cortiorgan des Versuchstieres lässt gegenüber dem des Kontrolltieres keine auffälligen Reaktionsunterschiede erkennen. Ganz ähnlich verhält sich die Stria vascularis, die bei den meisten Versuchstieren eine starke SH-Reak-

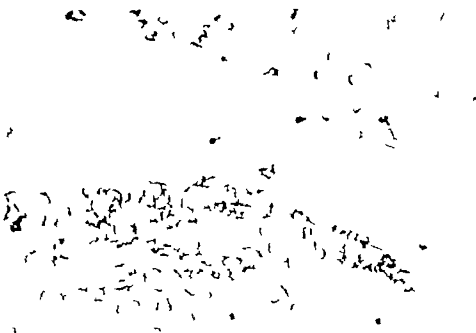


Abb. 7. Nachweis der unspez. Esterase im S. (Versuchstier). 480-fache Vergr.



Abb. 8. Nachweis der N-Acetyl-β-Glukosaminidase im S. e. (Kontrolltier). 480-fache Vergr.

tion aufweist, ohne dass wesentliche Reaktionsunterschiede gegenüber dem Kontrolltier auszumachen wären. Beim Vergleich von Kontroll- und Versuchstieren muss man bei der Intensität der histochemischen Reaktion davon ausgehen, dass geringfügige Quantitätsverschiebungen nur schwer eingeschätzt werden können.

4.5 Fermenthistochemische Befunde des Saccus endolymphaticus (S. e.)

4.5.1 *Unspezifische Esterase*

Beim Kontrolltier zeigt sich in der Pars intermedia eine mässig bis mittelstarke Fermentreaktion, die sich überwiegend am apikalen Pol der lumenwärts gerichteten Epithelien

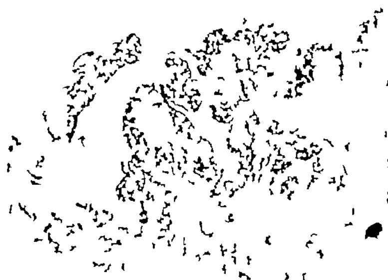


Abb. 9. Nachweis der N-Acetyl-Glukosaminidase im S. e. (Versuchstier). 480-fache Vergr.



Abb. 6. Nachweis der unspez. Esterase im Saccus endolymphaticus (Kontrolltier). 480-fache Vergr.

4.4 *Nachweis der Sulfhydryle und Gesamtsulfhydryle (SH+SS) in der Cochlea*

Beim Normaltier findet sich eine kräftige SH-Reaktion in den inneren und äusseren Haarzellen, in geringerem Ausmasse in den Pfeilerzellen sowie den Hensen- und Deiterszellen. Vergleiche mit der Reaktion der *Gesamtsulfhydryle* zeigen, dass die Farbintensität in der Stria vascularis relativ geringfügiger zunimmt als in den Zellen des sog. Stützsystems. Das Cortiorgan des Versuchstieres lässt gegenüber dem des Kontrolltieres keine auffälligen Reaktionsunterschiede erkennen. Ganz ähnlich verhält sich die Stria vascularis, die bei den meisten Versuchstieren eine starke SH-Reak-

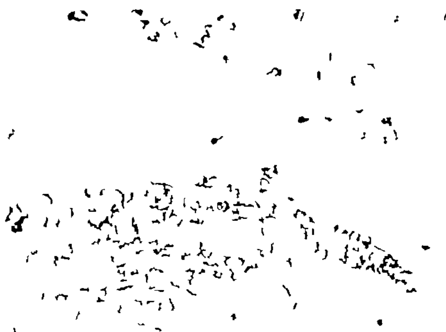


Abb. 7. Nachweis der unspez. Esterase im S. e. (Versuchstier). 480-fache Vergr.

ie Enzymreaktionen beim Versuchstier aus. Auch hier sind die Prädilektionsstellen des Enzyms die Epithelien der Pars intermedia und das subepitheliale Bindegewebe. Die Quantitätsschätzung der Fermente und deren Lokalisationsorte gehen aus Tab. 4 hervor.

4.6. Histochemischer Nachweis der Gluko-*Mukoproteide sowie saurer Mukosubstanzen*

4.6.1. *PAS-Alcianblau-Reaktion nach Runge et al. (1956)*

Mit dieser Färbemethode zeigt sich beim Kontroll- und Versuchstier eine intensive Anfärbung der Tectorialmembran, der Basilarmembran und deren Insertationsstellen am Limbus und Lig. spirale. Zudem wird in der bindegewebigen Grundsubstanz des Limbus spiralis eine deutliche, wenn auch schwächere Reaktion als z. B. in der Basilarmembran erkennbar.

Führt man eine Hyaluronidase-Vorbehandlung der Schnitte durch, nimmt die Anfärbbarkeit der Tectorialmembran, der Basilarmembran und des Bindegewebes von Limbus und Lig. spirale ab, d. h. es ist die Annahme berechtigt, dass an den beschriebenen Stellen saure hyaluronidasesensible Mukosubstanzen vorkommen. Durch zusätzliche Ribonukleasebehandlung wird die *Alcianophilie nicht* verändert.

Da jedoch auch nach *Hyaluronidase*-Vorbehandlung in der Tectorialmembran metachromatische Reaktionen ausgelöst werden können, dürfte diese Tatsache für die Anwesenheit anderer saurer Glukoproteide sprechen, deren Existenz in letzter Zeit immer mehr in den Vordergrund gestellt wird. PAS-positives amylaseresistentes Material findet sich im Lig. und Limbus spirale, in der Tectorialmembran, Basilarmembran, in verschiedenen Zellen des Stützsystems des Cortiorgans sowie in der Stria vascularis.

Auffällige Reaktionsunterschiede bei der PAS-Alcianblau-Färbung zwischen Kontroll- und Versuchstieren existieren nicht.

Während beim Kontrolltier der Perilymphraum (Scala tympani und Scala vestibuli) sowie der Ductus cochlearis bei verschiedenen Färbemethoden färberisch „leer" ist (Abb. 10), entdeckt man bei etwa der *Hälfte aller* Versuchstiere einen Niederschlag im Perilymphraum, manchmal auch im Endolymphraum, der sich mit PAS-Alcianblau leicht blau getönt darstellt. Die Abb. 11 zeigt die Scala tympani mit einem Niederschlag bei einem Versuchstier, welches 8 Wochen zuvor thyreoidektomiert wurde. Nach Einwirkung von Hyaluronidase lassen sich zwei Farbänderungen ausmachen (Abb. 12). Einmal nimmt die Anfärbung des im Perilymphraum gelegenen Niederschlages sehr deutlich ab, zum anderen ist auch die Farbintensität der Basilarmembran, des Limbus spiralis *und des Lig.* spirale am Insertationsort der Membrana basilaris reduziert.

Bei einem anderen Tier findet sich der Niederschlag in unmittelbarer Nähe des N. acusticus (Abb. 13), wobei man den Eindruck gewinnt, dass der Nerv zur anderen Seite etwas verdrängt wird. Wendet man hier die Hyaluronidasebehandlung des Schnittes an, so erkennt *man eine auffällige Abnahme der* Anfärbbarkeit des *Niederschlages (Abb. 14).*

Auf Abb. 15 sieht man im Bereich des Plexus cochlearis (Balogh und Koburg, 1965) eines arteriellen und venösen Gefässnetzes in der Umgebung des N. acusticus eine Ablagerung eines alcianophilen Niederschlages, der unter dem Einfluss von Hyaluronidase stark abnimmt (Abb. 16).

Zum anderen lässt sich im Bereich des beschriebenen Plexus cochlearis ein schwach PAS-positives Material nachweisen, welches sich erwartungsgemäss unter dem Hyaluronidaseeinfluss nicht verändert, sich darüber hinaus auch in seiner morphologischen Beschaffenheit von der *hyaluronidasesensiblen Substanz* in *Peri- und Endolymphräumen* sowie im Bereich des Plexus cochlearis unterscheidet.

Zu Kontrollzwecken wurden verschiedene *Methoden* angewendet. Durch Methylierung lässt sich mit der PAS-Alcianblaufärbung keine *Blaufärbung* – weder in den verschiedenen

Tabelle V *Fermentaktivitäten in verschiedenen Bereichen des Saccus endolymphaticus nach Thyreoidektomie*

	Esterase	Glukuronidase	Glukosaminidase	Sulfatase	Galaktosidase
Epithelien Pars intermedia	+0	++	+0–+	++	+
Epithelien Pars distalis	+0	+0	+0	+	+0
Bindegewebe	0	0	0	+0	+0
Zellen im Bdg.	0	0	+0	+0	+0
Sog. freie Zellen	+0–+	+0–+	+0–++	+–++	+0

nachweisen lässt, an einzelnen Epithelabschnitten stärker als an anderen ausgeprägt ist (Abb. 6). Dabei dürfen die nur in den Epithelien vorhandenen Pigmentkörnchen nicht mit den Enzymgranula verwechselt werden. Abb. 7 stellt den S. e. eines Versuchstieres dar, bei dem lediglich (im rechten unteren Bildrand) eine nur geringe Fermentaktivität auszumachen ist. Das Bindegewebe enthält kaum Fermentkörnchen. Einzelne sog. freie Zellen in der Saccuslichtung haben einen stärkeren Enzymgehalt.

4.5.2 β-Glukuronidase

Die Glukuronidase verhält sich hinsichtlich ihrer Aktivität in vergleichbaren Werten wie die Esterase. Beim Normaltier findet man schwache bis mittelstarke Enzymreaktionen in der Pars intermedia des S. e., weniger jedoch in der Pars distalis. Das Bindegewebe ist praktisch negativ. Einzelne sog. freie Zellen im Saccuslumen sind stärker positiv. Im Vergleich hierzu verändert sich das Enzymmuster beim Versuchstier nicht.

4.5.3 N-Acetyl-β-Glukosaminidase

Die Glukosaminidase weist in der Pars intermedia ein beträchtliches Reaktionsprodukt auf, ebenso findet sich auch in der Pars distalis eine erhebliche Enzymaktivität. Die Abb. 8 stellt einen Ausschnitt aus der Pars rugosa (Pars intermedia des S. e.) mit dem dunkel gefärbten Epithel dar, die sich lichtmikroskopisch als blaue Fermentkörnchen abzeichnen (Kontrolltier).

Im S. e. der Versuchstiere findet sich bei den meisten eine auffällige Fermentabnahme, wie dies Abb. 9 zeigt. Man sieht die Enzymkörnchen überwiegend im apikalen, der Saccuslichtung zugewandten Epithelbereich.

4.5.4 β-Galaktosidase

Galaktosidase und Glukuronidase verhalten sich in Enzymaktivität und Verteilungsmuster im Saccus endolymphaticus gleichermassen.

Sowohl beim Versuchstier als auch beim Kontrolltier erkennt man in den Epithelien der Pars intermedia mässige bis mittelstarke Enzymreaktionen, die in der Pars distalis deutlich geringer sind. Einzelne sog. freie Zellen in der Saccuslichtung enthalten ebenfalls Fermentgranula. Das subepitheliale Bindegewebe ist praktisch negativ, abgesehen von einzelnen bindegewebigen Zellen.

4.5.5 Nachweis der Aryl-Sulfatase

Die Sulfatase-Reaktion fällt von allen anderen untersuchten Fermenten am stärksten aus. Wie aus den Untersuchungen hervorgeht, zeigen sich zahlreiche Fermentgranula in den Epithelien der Pars rugosa, aber auch im subepithelialen Bereich des Kontrolltieres. Das Epithel der Pars distalis ist mässig positiv. Das Saccusbindegewebe reagiert unterschiedlich stark. An manchen Stellen findet man zahlreiche mit Fermentgranula beladene Fibrozyten und Histiozyten, andererorts ist das Bindegewebe fast negativ. Zudem kommen in der Saccuslichtung mit Fermentgranula beladene Zellen vor. Praktisch unverändert fallen

e Enzymreaktionen beim Versuchstier aus. uch hier sind die Prädilektionsstellen des nzyms die Epithelien der Pars intermedia nd das subepitheliale Bindegewebe. Die uantitätsschätzung der Fermente und deren okalisationsorte gehen aus Tab. V hervor.

1.6. Histochemischer Nachweis der Gluko-/Mukoproteide sowie saurer Mukosubstanzen

1.6.1 *PAS-Alcianblau-Reaktion nach Runge et al. (1956)*

Mit dieser Färbemethode zeigt sich beim Kontroll- und Versuchstier eine intensive Anfärbung der Tectorialmembran, der Basilarmembran und deren Insertationsstellen am Limbus und Lig. spirale. Zudem wird in der bindegewebigen Grundsubstanz des Limbus spiralis eine deutliche, wenn auch schwächere Reaktion als z.B. in der Basilarmembran erkennbar.

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Da jedoch auch nach Hyaluronidase-Vorbehandlung in der Tectorialmembran metachromatische Reaktionen ausgelöst werden können, dürfte diese Tatsache für die Anwesenheit anderer saurer Glukoproteide sprechen, deren Existenz in letzter Zeit immer mehr in den Vordergrund gestellt wird. PAS-positives amylaseresistentes Material findet sich im Lig. und Limbus spirale, in der Tectorialmembran, Basilarmembran, in verschiedenen Zellen des Stützsystems des Cortiorgans sowie in der Stria vascularis.

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Bei einem anderen Tier findet sich der Niederschlag in unmittelbarer Nähe des N. acusticus (Abb. 13), wobei man den Eindruck gewinnt, dass der Nerv zur anderen Seite etwas verdrängt wird. Wendet man hier die Hyaluronidasebehandlung des Schnittes an, so erkennt man eine auffällige Abnahme der Anfärbbarkeit des Niederschlages (Abb. 14).

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Zum anderen lässt sich im Bereich des beschriebenen Plexus cochlearis ein schwach PAS-positives Material nachweisen, welches sich erwartungsgemäss unter dem Hyaluronidaseeinfluss nicht verändert, sich darüberhinaus auch in seiner morphologischen Beschaffenheit von der hyaluronidasesensiblen Substanz in Peri- und Endolymphräumen sowie im Bereich des Plexus cochlearis unterscheidet.

Zu Kontrollzwecken wurden verschiedene Methoden angewendet. Durch Methylierung lässt sich mit der PAS-Alcianblaufärbung keine Blaufärbung – weder in den verschiedenen

Tabelle V *Fermentaktivitäten in verschiedenen Bereichen des Saccus endolymphaticus nach Thyreoidektomie*

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Epithelien Pars distalis	+0	+0	+0	+	+0
Bindegewebe	0	0	0	+0	+0
Zellen im Bdg	0	0	+0	+0	+0
Sog. freie Zellen	+0–+	+0–+	+0–++	+–++	+0

nachweisen lässt, an einzelnen Epithelabschnitten stärker als an anderen ausgeprägt ist (Abb 6) Dabei dürfen die nur in den Epithelien vorhandenen Pigmentkörnchen nicht mit den Enzymgranula verwechselt werden Abb 7 stellt den S e eines Versuchstieres dar bei dem lediglich (im rechten unteren Bildrand) eine nur geringe Fermentaktivität auszumachen ist. Das Bindegewebe enthält kaum Fermentkörnchen Einzelne sog. freie Zellen in der Sacculichtung haben einen stärkeren Enzymgehalt.

4 5 2 *β-Glukuronidase*

Die Glukuronidase verhält sich hinsichtlich ihrer Aktivität in vergleichbaren Werten wie die Esterase Beim Normaltier findet man schwache bis mittelstarke Enzymreaktionen in der Pars intermedia des S e weniger jedoch in der Pars distalis Das Bindegewebe ist praktisch negativ Einzelne sog. freie Zellen im Sacculumen sind stärker positiv Im Vergleich hierzu verändert sich das Enzymmuster beim Versuchstier nicht

4 5 3 *N Acetyl β-Glukosaminidase*

Die Glukosaminidase weist in der Pars intermedia ein beträchtliches Reaktionsprodukt auf ebenso findet sich auch in der Pars distalis eine erhebliche Enzymaktivität. Die Abb 8 stellt einen Ausschnitt aus der Pars rugosa (Pars intermedia des S e) mit dem dunkel gefärbten Epithel dar die sich lichtmikroskopisch als blaue Fermentkörnchen abzeichnen (Kontrolltier)

Im S e der Versuchstiere findet sich bei den meisten eine auffällige Fermentabnahme wie dies Abb 9 zeigt Man sieht die Enzymkörnchen überwiegend im apikalen der Saccuslichtung zugewandten Epithelbereich

4.5 4 *β-Galaktosidase*

Galaktosidase und Glukuronidase verhalten sich in Enzymaktivität und Verteilungsmuster im Saccus endolymphaticus gleichermassen

Sowohl beim Versuchstier als auch beim Kontrolltier erkennt man in den Epithelien der Pars intermedia mässige bis mittelstarke Enzymreaktionen die in der Pars distalis deutlich geringer sind Einzelne sog freie Zellen in der Saccuslichtung enthalten ebenfalls Fermentgranula. Das subepitheliale Bindegewebe ist praktisch negativ abgesehen von einzelnen bindegewebigen Zellen

4 5 5 *Nachweis der Aryl-Sulfatase*

Die Sulfatase Reaktion fällt von allen anderen untersuchten Fermenten am stärksten aus. Wie aus den Untersuchungen hervorgeht zeigen sich zahlreiche Fermentgranula in den Epithelien der Pars rugosa, aber auch im subepithelialen Bereich des Kontrolltieres Das Epithel der Pars distalis ist mässig positiv Das Saccusbindegewebe reagiert unterschiedlich stark An manchen Stellen findet man zahlreiche mit Fermentgranula beladene Fibrozyten und Histiozyten anderenorts ist das Bindegewebe fast negativ Zudem kommen in der Saccuslichtung mit Fermentgranula beladene Zellen vor Praktisch unverändert fallen

das Enzymreaktionen beim Versuchstier aus. Auch hier sind die Prädilektionsstellen des Enzyms die Epithelien der Pars intermedia und das subepitheliale Bindegewebe. Die Quantitätsschätzung der Fermente und deren Lokalisationsorte gehen aus Tab V hervor

4.6. Histochemischer Nachweis der Gluko-Mukoproteide sowie sauren Mukosubstanzen

4.6.1 *PAS-Alcianblau-Reaktion nach Runge et al (1956)*

Mit dieser Farbemethode zeigt sich beim Kontroll- und Versuchstier eine intensive Anfärbung der Tectorialmembran der Basilarmembran und deren Insertationsstellen am Limbus und Lig. spirale Zudem wird in der bindegewebigen Grundsubstanz des Limbus spiralis eine deutliche wenn auch schwächere Reaktion als z.B in der Basilarmembran erkennbar

Führt man eine Hyaluronidase-Vorbehandlung der Schnitte durch nimmt die Anfärbbarkeit der Tectorialmembran, der Basilarmembran und des Bindegewebes von Limbus und Lig. spirale ab d h es ist die Annahme berechtigt dass an den beschriebenen Stellen saure hyaluronidasesensible Mukosubstanzen vorkommen. Durch zusätzliche Ribonukleasebehandlung wird die Alcianophilie nicht verändert.

Da jedoch auch nach Hyaluronidase-Vorbehandlung in der Tectorialmembran metachromatische Reaktionen ausgelöst werden können dürfte diese Tatsache für die Anwesenheit anderer saurer Glukoproteide sprechen deren Existenz in letzter Zeit immer mehr in den Vordergrund gestellt wird PAS-*positives* amylaseresistentes Material findet sich *im* Lig und Limbus spirale in der Tectorial*membran Basilarmembran* in verschiedenen Zellen des Stützsystems des Cortiorgans sowie in der Stria vascularis

Auffällige Reaktionsunterschiede bei der PAS-Alcianblau-Farbung zwischen Kontroll- und Versuchstieren existieren nicht.

Während beim *Kontrolltier der Perilymph*raum (Scala tympani und Scala vestibuli) sowie der Ductus cochlearis bei verschiedenen Färbemethoden färberisch „leer" ist (Abb 10) entdeckt man bei etwa der Hälfte aller Versuchstiere einen Niederschlag im Perilymphraum, *manchmal* auch im Endolymphraum der sich mit PAS-Alcianblau leicht blau getönt darstellt. Die Abb 11 zeigt die Scala tympani *mit einem* Niederschlag bei einem Versuchstier welches 8 Wochen zuvor thyreoidektomiert wurde. Nach Einwirkung von Hyaluronidase lassen sich zwei *Farbän*derungen ausmachen (Abb 12) Einmal nimmt die Anfärbung des im Perilymphraum gelegenen Niederschlages sehr deutlich ab zum anderen ist auch die Farbintensität der Basilarmembran des Limbus spiralis und des Lig. spirale am Insertationsort der Membrana basilaris reduziert.

Bei einem anderen Tier findet sich der Niederschlag in unmittelbarer Nähe des N acusticus (Abb 13) wobei man den Eindruck gewinnt dass der Nerv zur anderen Seite etwas verdrängt wird Wendet man hier die Hyaluronidasebehandlung des Schnittes an, *so erkennt man eine auffällige Abnahme der* Anfärbbarkeit des Niederschlages (Abb 14)

Auf Abb 15 sieht man im Bereich des Ple*xus cochlearis (Balogh und Koburg, 1965)* eines arteriellen und venösen Gefässnetzes in der Umgebung des N acusticus eine Ablagerung eines *alcianophilen Niederschlages* der unter dem Einfluss von Hyaluronidase stark abnimmt (Abb 16)

Zum anderen lässt sich im Bereich des beschriebenen Plexus cochlearis ein schwach PAS-positives Material nachweisen welches sich erwartungsgemäss unter dem Hyaluronidaseeinfluss nicht verändert, sich darüberhinaus auch in seiner morphologischen Beschaffenheit von der hyaluronidasesensiblen Substanz in Peri und Endolymphräumen sowie im Bereich des Plexus cochlearis unterscheidet.

Zu Kontrollzwecken wurden verschiedene Methoden angewendet. Durch Methylierung lässt sich mit der PAS-Alcianblaufärbung *keine* Blaufärbung – weder in den verschiedenen



Abb 10 PAS-Alcianblau-Reaktion der Scala tympani (Kontrolltier). 150-fache Vergr

Gewebsbereichen noch in den Niederschlägen – erzielen Durch Sulfatierung wird keine vermehrte Blaufärbung erreicht Bei Hyaluronidase Vorbehandlung nimmt – wie schon mehrfach erwähnt – die Anfärbbarkeit der Basilarmembran der Tectorialmembran und des Limbus spiralis sowie des Lig. spirale ab Ein ähnliches Verhalten wenn auch in stärkerem Ausmasse lassen die Niederschläge im Peri und Endolymphraum erkennen Bei der Ribonuklease Anwendung kann man lediglich im Zytoplasma der Ganglienzellen eine starke Verringerung der Anfärbbarkeit auslösen

4 6 2 *Eisenbindungsreaktion nach Hale (1946) in der Modifikation nach Graumann und Clauss (1958) oder PAS Hale nach Ritter und Oleson (1950)*

Basilarmembran und deren Ansatzstellen am Limbus spiralis und Lig. spirale sowie die Tectorialmembran färben sich intensiv an

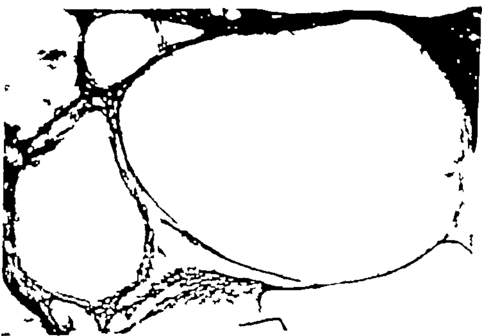


Abb 11 PAS-Alcianblau Reaktion der Scala tympani ohne Hyaluronidase Vorbehandlung (Versuchstier) 150-fache Vergr



Abb. 12 PAS-Alcianblau-Reaktion der Scala tympani desselben Versuchstieres wie Abb. 11 mit Hyaluronidase Vorbehandlung. 150-fache Vergr.

ähnlich verhält sich auch die Stria vascularis. Der Limbus spiralis weist eine kräftigere Reaktion im Bereiche der Huschkeschen Hörzähne auf. Das Cortiorgan ist negativ. Auch bei dieser Methode finden sich keine ins Gewicht fallenden Farbunterschiede zwischen Kontroll- und Versuchstier.

Vergleichbar jedoch der Alcianblauffärbung lassen sich auch in den Skalen und im Bereich des Plexus cochlearis Niederschläge aufzeigen, deren Anfärbbarkeit unter dem Einfluss von Hyaluronidase abnimmt, d.h. also, dass hier ein hyaluronidasesensibles Substrat vorliegt. Ribonuklease-Behandlung des Schnittes beeinflusst die Farbintensität nicht.

4.6.3 *Metachromasie-Reaktionen*

4.6.3.1 *Azur-A bei verschiedenen pH Werten*

Wie aus der Tabelle Nr. 6 hervorgeht, sieht man in der Cochlea bei pH 4,5 eine starke



Abb. 13 PAS-Alcianblau-Reaktion in Nähe des N. acusticus ohne Hyaluronidasebehandlung (Versuchstier). 150-fache Vergr.



Abb. 14. PAS-Alcianblau-Reaktion desselben Versuchstieres wie in Abb. 13 mit Hyaluronidasebehandlung. 150-fache Vergr.

Metachromasie-Reaktion der Tectorialmembran, der Basilarmembran und des Knochens des Modiolus. Auch das Verankerungssystem der Basilarmembran im Limbus spiralis und Lig. spirale reagieren metachromatisch, ebenso eine dreieckige Zone oberhalb des Ansatzes der Basilarmembran am Lig. spirale. Das Cortiorgan und die tympanale Belegschicht lassen sich nur orthochromatisch anfärben. Die Reissner-Membran reagiert schwach metachromatisch, die beschriebenen Niederschläge in den Skalen, im Ductus cochlearis sowie im Bereich des Plexus cochlearis der Versuchstiere verhalten sich weitgehend orthochromotrop.

Bei pH 3 tritt ein Farbumschlag der Niederschläge ein, d. h. bei diesem pH-Wert wird eine Metachromasie-Reaktion ausgelöst. Im übrigen verhalten sich auch bei diesem pH-Wert die Tectorialmembran, die Basilarmem-



Abb. 15. PAS-Alcianblau-Reaktion des Plexus cochlearis ohne Hyaluronidasebehandlung (Versuchstier). 150-fache Vergr.

Tabelle VI *Zusammenfassung der Metachromasie-Reaktionen an verschiedenen Abschnitten der Cochlea des thyreoidektomierten Tieres*

	Gluko-Mukoproteide Saure Mukosubstanzen PAS-Alcianblau	Saure Mukosubstanzen Azur A			Saure Mukosubstanzen Toluidinblau			Gluko-Mukoproteide Saure Mukosubstanzen Eisenbindungsreaktion
		pH 1,5	pH 3,0	pH 4,5	0,4 m	0,2 m	0,04 m	
Stria vasc.	0	Orthochromasie	orth. (0)	orth.	Orthochromasie	0	0	+–++
Sulc. spir. ext.	0					+		
Lig. spirale	0–+		orth.	+0			+0	+0
Ggl. spirale	0		++	+		++	++	+0
Äußere HZ	0			0		0	0	0
Innere HZ	0			0		0	0	0
Deiters Zellen	0			0		0	0	0
Hensen Zellen	0			0		0	0	0
Pfeiler Zellen	0			0		0	0	0
Memb. tect.	+		+	++		++	++	++
Reissner M.	+0			0		0	0	0
Basil. M.	+			++		++	++	++
Tymp. Belegsch.	0			0		0	0	0
Limb. spirale	+0–		+0	+		+0	+	+
N. acusticus	0							
Prosangiosum F.	0							
Endolymph.-Raum	+					+	+	+
Perilymph. Raum	+		+			+		++
Gefäß-Bdg. Modiolus				+		++	+	+
Knochengrundsubst.			++	+		++	+	+

–Großteils unspezifische Rotung

bran und deren Verankerungssystem sowie der Knochen im Modiolus deutlich metachromatisch. Cortiorgan und Stria vascularis sowie die tympanale Belegschicht zeigen nur Orthochromasie.

Bei pH 1,5 treten in der Cochlea fast nur orthochromatische Reaktionen auf.

Durch Ribonuklease-Vorbehandlung der Schnitte wird die Metachromotropie des Gewebes nicht auffällig verändert. Durch Hyaluronidase lässt sich eine geringfügige Abnahme der Metachromotropie in der Tectorialmembran ausmachen. In stärkerem Ausmasse lässt der metachromatische Effekt in den alcianophilen Niederschlägen der Versuchstiere nach.

4.6.3.2 *Toluidinblau bei abgestuften CaCl-Konzentrationen.* Bei 0,04 M Toluidinblau-Lösung erkennt man keine Metachromasie; es fällt lediglich eine unspezifische Rotfärbung fast aller Cochleastrukturen auf.

Mit der 0,1 M Lösung zeigen sich gleichfalls noch keine auffälligen Farbumschläge in den verschiedenen Innenohrstrukturen, was auf eine Metachromasie-Reaktion schliessen lassen könnte. Bei den Versuchstieren verhalten sich die beschriebenen Niederschläge orthochromatisch.

Erst bei 0,2 M Toluidinblau-Lösung kann man Metachromasie-Reaktionen feststellen, wie sie sich etwa bei der Azur A Färbung pH 3,5 beobachten lassen. Tectorialmembran und Basilarmembran färben sich rot an, eben so verhalten sich die bindegewebigen Areale des Verankerungssystems der Basilarmembran. Cortiorgan, tympanale Belegschicht, Reissner Membran, Stria vascularis verhalten sich orthochromatisch. Im Vergleich dieser Innenohrstrukturen ergeben sich keine bemerkenswerten Unterschiede zwischen Kontroll- und Versuchstieren.

Die nur bei den Versuchstieren zu beobachtenden Niederschläge in den Skalen im Bereich des Plexus cochlearis lassen eine eindeutige Metachromasiereaktion erkennen. Sie stellen sich bei der 0,3 M Lösung rot dar



Abb 16 PAS-Alcianblau-Reaktion desselben Versuchstieres mit Hyaluronidasebehandlung. 150-fache Vergr

Als Kontrollreaktionen wurden die gleichen Verfahren angewendet wie bei der Azur A Methode (Hyaluronidase Ribonuklease) Die verschiedenen Metachromasieresultate sind der Tab VI zu entnehmen

4 7 Histochemischer Nachweis der Gluko-Mukoproteide sowie sauren Mukosubstanzen im Saccus endolymphaticus

4 7 1 PAS *Alcianblau Reaktion nach Runge et al (1956)*

Mit dieser Methode lässt sich eine mittelstarke Reaktion im Bindegewebe besonders im subepithelialen Bereich der Pars intermedia (Pars rugosa) des Normaltieres darstellen Ebenso färbt sich das Zytoplasma einzelner grösserer Bindegewebszellen an Das Epithel verhält sich praktisch negativ Bei dem Normaltier färbt sich der Inhalt des Saccus endolymphaticus mit der PAS Alcianblau Reaktion kaum oder gar nicht an während er sich bei der Hämatoxilin Eosin Anfärbung schwach rot darstellt. Bei einigen Versuchstieren lässt sich ein Saccusinhalt beobachten der sich mit PAS Alcianblau schwach blau darstellt Ausser diesem alcianophilen Saccusinhalt besteht kein signifikanter Farbunterschied in den einzelnen Strukturen des Saccus endolymphaticus zwischen Kontroll und Versuchstier

Wendet man zu Kontrolluntersuchungen Hyaluronidasebehandlung des Schnittes an so zeigt sich dass der Inhalt des Saccuslumen z T hyaluronidasesensibel ist d h die Anfärbbarkeit des Materials herabgesetzt wird Unter Ribonuklease Einwirkung wird das Zytoplasma der Bindegewebszellen praktisch farblos darüberhinaus ändert sich der Farbton der alcianblaupositiven Substanzen nicht

4 7 2 *Eisenbindungsreaktion nach Hale (1946) in der Modifikation nach Graumann und Clauss (1958) oder PAS Hale nach Ritter und Oleson (1950)*

Hier ergeben sich praktisch die gleichen Ergebnisse wie bei der PAS-Alcianblaufärbung Es färbt sich in besonderem Masse das Bindegewebe des S e an was besonders im subepithelialen Bereich der Pars intermedia in Erscheinung tritt Das Epithel ist kaum angefärbt schwach reagiert das Zytoplasma ein

zelner sog. freier Zellen in der Saccuslichtung. Bei einigen Versuchstieren färbt sich auch der Inhalt des Saccus leicht an. Der Farbton verschwindet unter dem Einfluss von Hyaluronidase weitgehend. Bei anderen Versuchs- und Kontrolltieren wird der schwach blau gefärbte Saccusinhalt durch Hyaluronidase in seiner Anfärbbarkeit nicht beeinflusst.



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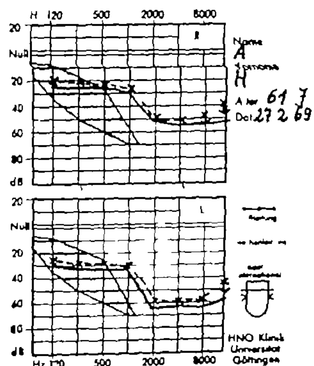
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5 Eigene klinische Beobachtung von hypothyreotisch bedingten Hörstörungen

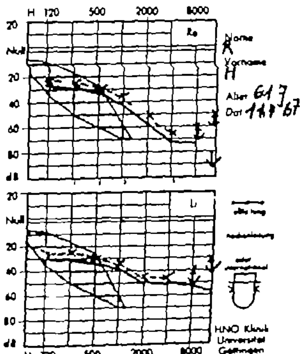
In der Poliklinik der Hals-Nasen-Ohrenklinik Göttingen konnten wir in der letzten Zeit zwei Patienten untersuchen, die an einer Unterfunktion der Schilddrüse in Verbindung mit einer rasch zunehmenden Hörstörung litten.

Bei einem 61jährigen Patienten (H. A.) stellte sich 3–4 Monate zuvor eine zunehmende Heiserkeit ein, gleichzeitig bemerkte er ein deutliches Nachlassen des Hörvermögens. Bei der Untersuchung in der Medizinischen Klinik in Göttingen wurde die Diagnose „Myxoedem bei einer Hashimoto-Thyreoiditis" gestellt. Die Untersuchung der Ohren erbrachte bds. völlig reizlose Trommelfelle, die Tubenfunktion war regelrecht. Die elektronakustische Hörprüfung zeigte eine beiderseitige Innenohrstörung, wobei hauptsächlich die hohen Frequenzen (1 000–8 000 Hz) betroffen waren. Die ohrenärztliche Diagnose lautete: Schallempfindungsstörung bds. bei Unterfunktion der Schilddrüse.

Eine 61jährige (R. H.) bemerkte seit über 1 Jahr eine „Schwellung der Haut", Müdigkeit, Konzentrationsschwäche. Ausserdem stellte sie eine immer mehr zunehmende Schwerhörigkeit fest. Die Pat. wurde wegen einer primären Hypothyreose stationär behandelt und zur Überprüfung des Hörvermögens der Hals-Nasen-Ohrenklinik vorgestellt. In der Anamnese gab sie an, bis vor 1 Jahr gut gehört zu haben, gleichzeitig, mit Zunahme der Hautschwellung habe sich das Gehör immer mehr verschlechtert. Die otoskopische Untersuchung ergab völlig reizlose intakte Trommelfelle. Die elektroakustische Hörprüfung zeigte eine beiderseitige Innenohrstörung im gesamten Frequenzbereich, die links etwas stärker als rechts ausgeprägt war. Diagnose: Bds. Schallempfindungsstörung bei Unterfunktion der Schilddrüse.



Audiogramm I (H. A.) Innenohrschwerhörigkeit bds besonders im Hochtonbereich



Audiogramm II (R. H.) Innenohrschwerhörigkeit im gesamten Frequenzbereich links stärker als rechts

6 Hörstörungen in Verbindung mit Schilddrüsenerkrankungen

6.1 Endemischer Kretinismus und Pendred-Syndrom

Zahlreiche Publikationen aus der Mitte des vorigen Jahrhunderts bis in die jüngste Zeit haben sich mit der Frage nach dem *Funktionszusammenhang zwischen Schilddrüse und Ohr* beschäftigt. Nach Kenntnis der Literatur kann man sich jedoch nicht des Eindruckes erwehren, dass die möglichen Zusammenhänge eher unübersichtlich und in ihrer Interpretation recht verschiedenartig dargestellt sind. Im folgenden soll daher ein kurzer Überblick über die Schilddrüsenerkrankungen gegeben werden, die mit Hörstörungen einhergehen können oder bei denen die Schwerhörigkeit obligater Bestandteil der Erkrankung ist.

Seit langem ist bekannt, dass die bei endemischen Kretinen zu beobachtende Schwerhörigkeit oder Taubstummheit häufig vorkommt, ohne jedoch obligates Symptom der Schilddrüsenerkrankung zu sein. Ebenso ist die Verbreitung von Gehörstörungen nicht gleichzusetzen mit der Häufigkeit des endemischen Kretinismus oder der Intensität der Kropfendemien (Trotter 1960; Greenwald 1960; Costa und Ferraris 1963). Nach Osinowski (1962) haben 35% der Kretins eine nicht reversible Schwerhörigkeit bis Taubstummheit.

Manche Autoren bestreiten überhaupt einen direkten Zusammenhang zwischen der Schilddrüse und dem Ohr. Sie führen hierfür als Beweis an, dass Kinder mit angeborener Hypothyreose fast nie eine Hörstörung aufweisen. Sie stehen damit im Gegensatz zu *Prader (1957)*, der bei kindlichen Hypothyreosen häufiger *eine gewisse Schwerhörigkeit* feststellte. Letztlich muss betont werden, dass die Gehörstörungen beim endemischen Kretinismus durch Hormonsubstitution nicht zu beseitigen sind.

Zahlreiche *pathologisch-anatomische Arbeiten befassen sich mit dem Hörorgan von endemischen Kretins*, deren Ergebnisse auf eine Schalleitungsstörung schliessen lassen müssten (Siebenmann, 1904; Manasse 1909; Schlittler 1917; Nager 1917; Mayer 1919; Oppikofer 1921; Steurer *1922a, b*). Die meisten audiologischen *Untersuchungsergebnisse*, soweit sie bei den oft debilen Patienten auszuwerten sind, deuten aber auf einen schweren Innenohrschaden und weniger häufig auf eine Schalleitungsschwerhörigkeit hin (Lüscher 1948; König 1968 u. a.). Als pathologisches *Substrat der Schwerhörigkeit* wurden *Verengerung der Fensternischen*, Verklumpung der Gehörknöchelchen, Verdickung der Paukenschleimhaut und schlecht pneumatisierte Warzenfortsätze angegeben. Andere und dieselben Autoren wie Siebenmann (1906), Denker (1909), Alexander (1909, 1919), Oppikofer (1913), Habermann (1909), Brock (1970) und Nager (1921) fanden bei entsprechenden Autopsien keine Mittel- oder Innenohrveränderungen. Wegen der Schwierigkeit der Durchführung von elektroakustischen *Hörprüfungen* bei den oftmals oligophrenen Patienten ist es nicht verwunderlich, wenn bislang *nur relativ wenig* entsprechende *Untersuchungen gemacht* wurden. Versucht man eine zusammenfassende Darstellung der Hörstörungen in Verbindung *mit dem endemischen Kretinismus zu geben*, lassen sich vielleicht folgende Gesichtspunkte herausstellen:

a) Die Gehördefekte *kommen fast nur in* Gebieten mit endemischem Kretinismus vor und stellen *eines* der regelmässigsten *Symptome im Ablauf* dieser Erkrankung dar.

b) Kropf-Endemien mit endemischem Kreti-

nismus werden meist in abgelegenen Gegenden beobachtet. Daher ist es infolge Inzucht durchaus möglich, dass eine nicht durch den endemischen Kretinismus bedingte Taubstummheit vermehrt auftreten kann (Hanhart 1924, Secrétan 1954, Clements 1958).

c) König weist darauf hin, dass rezessive nicht endemische Formen der kongenitalen Taubstummheit, das Pendred Syndrom sowie Embryopathien (Rubeolen) als Ursache für die Hörstörung berücksichtigt werden müssen, wenn man Zusammenhänge zwischen dem endemischen Kretinismus und ihn begleitenden Hörstörungen beurteilen will.

d) Die Häufigkeit der Hörstörung als Symptom des endemischen Kretinismus wechselt von Endemiegebiet zu Endemiegebiet, was aus den Untersuchungen von McCarrison (1908), Greenwald (1960), McCullagh (1963), Srinivasan et al. (1964) sowie Choufoer et al. (1965) hervorgeht.

Eine weitere Schilddrüsenerkrankung, die *in Verbindung mit einer oft sehr erheblichen Innenohrstörung auftritt*, ist das sog. Pendred Syndrom, ein autosomal rezessiv vererbbares Leiden. Der Grad der Schwerhörigkeit und das Ausmass des Kropfes sind unterschiedlich. Nach Fraser (1964) liegt eine progressive Schallempfindungsstörung vor, deren Ursache *in der Cochlea zu lokalisieren* ist und die zumeist die hohen Tonfrequenzen betrifft. Die Schilddrüsenstörung beruht auf einem Defekt der Jodoxydation im Sinne einer Jodverwertungsstörung, die man auch bei anderen Schilddrüsenerkrankungen beobachten kann. Die Hypothyreose ist häufig nicht sehr deutlich ausgeprägt.

6.2 Primäre Hypothyreose infolge quantitativer Störung der Hormonbildung

Ebenfalls ist eine *Hörstörung bei Patienten* mit erworbener Hypothyreose bekannt. Durch Hormonsubstitution lässt sich oftmals das Hörvermögen bessern bzw. normalisieren. Die Art der Schwerhörigkeit und die Häufigkeit des Auftretens bei erworbener Hypothyreose wird von den Autoren recht unterschiedlich beurteilt. King (1907) beschrieb eine intermittierende Hypothyreose bei einem Erwachsenen mit rezidivierender Schwerhörigkeit, die sich durch Hormonsubstitution besserte. Mutmasslich handelte es sich um eine Innenohrstörung.

Kemp (1907) stellte bei einem Erwachsenen mit einer im späteren Lebensalter erworbenen Unterfunktion der Schilddrüse eine Schwerhörigkeit fest, die er auf ein verdicktes Trommelfell bezieht. Durch Hormonsubstitution besserte sich das Gehör.

Unter 3 hypothyreotischen Patienten fand Kellner (1922) *einen Kranken mit Schwerhörigkeit*, die er als eine Schalleitung diagnostizierte und auf ein Myxoedem der Paukenschleimhaut bezog.

Moehlig (1927) beschreibt erstmals hypothyreotische Patienten, die an einer leider nicht näher klassifizierten Schwerhörigkeit in *Kombination mit Schwindelzuständen litten.* Er konnte diese Störung bei 24 Patienten nachweisen. Als Erklärung erwägt der Autor einen Hydrops des Labyrinthes ähnlich wie beim Morbus Menière, ohne jedoch nähere Angaben über die Gründe seiner Vermutung zu machen.

Drury (1927) berichtete über 2 Patienten mit Hypothyreose, die an einer Schwerhörigkeit litten. *Um welche Form der Schwerhörigkeit* es sich handelte, wird nicht angegeben.

Von 6 Kranken mit Hypothyreose litt nach den Angaben von Mann (1929) nur einer an einer Schallempfindungsstörung, die sich zudem noch einseitig manifestierte. Auf Hormonsubstitution indessen besserte sich die Hypacusis.

1931 berichtete der gleiche Autor über 4 *weitere Fälle mit Myxoedem* und Hörstörung. In dieser Publikation ist nur von einem Patienten *mit Hörstörung die Rede.*

McLaurien (1945) betont, dass er bei einem hypothyreotischen *Patienten eine Hörstörung* bemerkte, *die sich durch keinen krankhaften* Befund am Trommelfell *erklären liess.* *Leider*

versäumte *auch dieser* Autor eine audiometrische Untersuchung.

Barnes (1947) untersuchte über 45 Myxoedemkranke, die angeblich alle eine Schalleitungsstörung aufwiesen. Aus dieser Arbeit gehen keine näheren Angaben über otoskopische Befunde hervor.

Marquet (1956) nimmt eine langsame Entstehung der Hörstörung bei erworbenen Hypothyreosen an und führt deren Entstehung auf ein „Oedem zwischen den Zellen" zurück. In dieser Arbeit wird nicht streng zwischen der Hörstörung beim endemischen Kretin und der Hörstörung des später hypothyreotisch gewordenen Patienten getrennt. Nach Angaben von Marquet (1956) lag zumeist eine Schallempfindungsstörung vor.

Hilger (1956) veröffentlichte die Krankheitsgeschichten von 4 hypothyreotischen Patienten, von denen drei an einer Schallempfindungsstörung und einer an einer Schalleitungsstörung litt. Das Hörvermögen war nach den audiometrischen Untersuchungen im gesamten Frequenzbereich gestört. Nach Hormonsubstitution erfolgte eine Besserung des Hörvermögens, was auch audiometrisch belegt werden konnte.

Howarth und Lloyd (1956) hatten *7* hypothyreotische Patienten untersucht und fanden *5* mit einer Schallempfindungsstörung und 2 mit einer Schalleitungsstörung. Bei 6 Patienten besserte sich das *Hörvermögen* durch Hormonsubstitution.

Die grösste Anzahl von hypothyreotischen Patienten mit Hörstörungen untersuchten Nickel und Frame (1958). 31 ihrer 100 Kranken liessen eine Schwerhörigkeit erkennen, über deren Art jedoch keine näheren Angaben gemacht werden.

Ritter und Lawrence (1960) untersuchten einen Patienten, der durch hohe Thiouracilgaben hypothyreotisch geworden war, und einen zweiten, der an einer primären idiopathischen Hypothyreose litt. Bei beiden Patienten bestand eine Schallempfindungsstörung, die durch Hormonsubstitution gebessert werden konnte.

De Vos (1963) berichtete in einer längeren sehr sorgfältig durchgeführten Arbeit über 37 Kranke mit erworbener Hypothyreose, von denen 10 eine Schwerhörigkeit vom Typ der Schallperzeptionsstörung aufwiesen. Aus dem Fehlen des Recruitmentphänomens schloss de Vos, dass das Cortiorgan als Ursprungsort für die Schwerhörigkeit auszuschliessen ist. Durch Hormongaben konnte er keine auffällige Besserung des Hörvermögens erzielen.

Post (1964) verfolgte die Krankheitsverläufe von 47 hypothyreotischen Patienten. Unter diesen Kranken gaben lediglich 4 eine Hörstörung an. Drei weitere Patienten mit einer Lärmschädigung des Innenohres und 3 mit einer bereits vor dem Auftreten der Hypothyreose diagnostizierten Schallempfindungsstörung wiesen keine weitere Verschlechterung des Hörvermögens auf.

Dennhardt (1965) behandelte 2 Patienten, bei denen neben einer Unterfunktion der Schilddrüse mit Myxoedem eine audiometrisch nachgewiesene Schalleitungsstörung vorlag. Diese Schwerhörigkeit besserte sich durch Hormongaben.

Stellt man die mitgeteilten Kasuistiken in einer Tabelle zusammen (Tab. Nr. 7), so gewinnt man den Eindruck einer gewissen Uneinheitlichkeit in dem klinischen Untersuchungsergebnis zum Problem erworbene Hypothyreosen – Hörstörung. Bei den aufgeführten Patienten hatte sich aus verschiedenen Gründen die Hypothyreose im Jugend- oder Erwachsenenalter manifestiert. Man darf wohl davon ausgehen, dass eine primäre Hypothyreose vorlag. Von den insgesamt 275 Patienten litten 141 an einer Schwerhörigkeit, deren Einteilung in die Schalleitungs- und Schallempfindungsstörung leider nicht von allen Autoren berücksichtigt wurde. Die Publikation von *Barnes (1947)* – er hatte bei 45 hypothyreotischen Patienten 45 Schalleitungsstörungen *festgestellt* – muss wohl mit Zurückhaltung beurteilt werden, da er keine genauen *otoskopischen* Befunde anführt. Seine Angaben stehen auch in einem Widerspruch zu allen anderen Autoren, wie aus Tab. 7 er-

Tabelle VII *Zusammenstellung der in der Literatur mitgeteilten Fälle von hypothyreotisch bedingter Schwerhörigkeit (primäre Hypothyreose)*

Autoren	Fälle mit erworbener Hypoth	Schallempfindungsstörung	Schalleitungsstörung	Nicht näher def Schwerhörigkeit
Kemp (1907)	1	1		
King (1907)	1	1		
Keßner (1922)	3		1	
Moehlig (1927)	4			4
Drury (1927)				
Mann (1929)	6	1 (einseitig)		
Mann (1931)	4		1	
Mc Laurien (1945)	1			1
Barnes (1947)	45		45(!)	
Rau (1947)	1	1		
Hilger (1956)	4	3	1	
Howarth + Lloyd (1956)	7	6		
Nickel + Frame (1958)	100			31
Ritter + Lawrence (1960)	2			
De Vos (1963)	3	15		
Post (1964)	4	3		
Dennhard (1965)				

sichtlich ist Ohne Berücksichtigung der Arbeit von Barnes (1947) und der Publikationen in denen die Form der Hörstörung nicht mitgeteilt wurde erhält man ein Verhältnis Schallempfindungsstörung / Schalleitungsstörung von 33 7 bei insgesamt 129 hypothyreotischen Patienten Diese Zahl stimmt in etwa mit den Angaben von Means (1948) überein der bei der primären erworbenen Hypothyreose 30% Schwerhörigkeit feststellte

Hinsichtlich der Entstehung der hypothyreotisch bedingten Schwerhörigkeit werden folgende Ansichten geäussert

McMahon (1947) nimmt eine durch den Thyroxinmangel hervorgerufene Minderung der Resistenz gegenüber Infektionen in woraus sich Otitiden und Tubenkatarrhe entwikkeln können Aus einem solchen Befund könnte eine Schalleitungsstörung resultieren Bei der Herabsetzung der Schallempfindung diskutiert der Autor eine zentrale Schädigung hält jedoch auch einen Hydrops der Schnecke für möglich Marquet (1956) betont das Fehlen des Recruitmentphänomens bei der hypothyreotischen Innenohrstörung und leitet daraus ab dass ursächlich eine Alteration des Cortiorgans nicht in Frage kommen kann Die Schwerhörigkeit entsteht nach Ansicht des Autors durch ein Ödem zwischen den Zellen mutmasslich zwischen den Zellen des Ganglion spirale Marquet führt 3 Gesichtspunkte an a) durch den Schilddrüsenmangel kommt es zu einer ödematösen Infiltration des endolymphatischen Kreislaufes und dadurch zu einer Perineuritis des Hörnerven (=typische Schallempfindungsstörung) b) Myxomatöse Läsionen im Mittelohr (=Schalleitungsstörung) c) Minderung des zentralen Hörvermögens

Ritter und Lawrence (1960) erwägen als Ursache für die Schwerhörigkeit eine durch den Thyroxinmangel ausgelöste ödematöse cochleare Veränderung wie sie auch in ähnlicher Weise von Marquet (1956) in den Vordergrund gestellt wird

De Vos (1963) kommt auf Grund seiner klinischen und experimentellen Arbeiten zu dem Ergebnis dass die hypothyreotisch bedingte Schwerhörigkeit auf einer Störung im Bereich des Ganglion spirale mit einer zusätzlich möglichen cerebralen Beeinträchtigung beruht Auch er betont das Fehlen des Recruitmentphänomens (wie Marquet 1956) und leitet daraus den Schluss ab dass eine direkte Schä

digung des Cortiorgans nicht in Betracht gezogen werden kann, sondern vielmehr im Bereich des Ganglion scarpae und des N. acusticus zu suchen ist.

Post (1964) hält cochleäre Ursachen für die Schallempfindungsstörung möglich, betont darüberhinaus, dass nach seinen klinischen Untersuchungen keine spezifische Verbindung zwischen dem Alter der Kranken, dem Grad der Hypothyreose und der daraus resultierenden Schwerhörigkeit existiert. Manche Patienten mit schwerer Hypothyreose haben keine Schwerhörigkeit, andere mit leichter Schilddrüsenunterfunktion eine sehr deutliche Schallempfindungsstörung.

Letztlich erwägt Dennhardt (1965) eine durch die Hypothyreose verursachte Verschiebung von Glukoproteiden und sauren Mukopolysacchariden im Innenohr, obwohl die von ihm beobachteten hypothyreotischen Patienten an einer Schalleitungsstörung litten.

Die angeführten Vorstellungen zur Genese der hypothyreotischen Schwerhörigkeit sind zumeist weitgehend unbewiesen und beruhen auf Analogieschlüssen, sieht man von ganz wenigen, später noch anzuführenden experimentellen Arbeiten (Poulsen 1959; de Vos, 1963; Ritter 1967) ab. Alle angeführten Denkmodelle erscheinen einleuchtend, wenn es sich um die Erklärung der Schalleitungsstörung handelt. Die Schallempfindungsstörungen stossen jedoch hinsichtlich ihrer Interpretation auf wesentlich grössere Schwierigkeiten.

7 Grundlagen zur Synthese, Produktion, Wirkungsweise und biologischen Wirkung der Schilddrüsenhormone

Die Hauptaufgabe der Schilddrüse besteht in der Synthese und Inkretion der beiden Hormone L Thyroxin und L Trijodthyronin Für die Synthese der Schilddrüsenhormone wird das Spurenelement Jod benötigt welches als ionales Jod im Blut entnommen und in eine besondere organische Bindung eingebaut wird Das entstandene Produkt muss danach gespeichert und im Bedarfsfall in Aminosäureform abgegeben werden können Der thyreoidale Jodumsatz stellt die spezielle Leistung der Schilddrüse dar Er verläuft in 5 Phasen die *in Anlehnung* an Klein (1969) summarisch wiedergegeben werden sollen

a) Jodination d h Jodanreicherung aus dem Blut im Schilddrüsengewebe

b) Jodisation d h Jodierung des in der Follikelzelle und im Kolloid vorhandenen Tyrosin zu sog. inaktiven Hormonvorläufern (Tyrosin zu 3 Monojodtyrosin 3-Mono- zu 3,5-Dijodtyrosin)

c) Koppelung von Jodtyrosin zu Jodthyroxin

d) Das Jodthyreoglobulin des Kolloids stellt das thyreoidale Jodreservoir dar Es enthält sämtliche organische Jodverbindungen der Schilddrüse ca $^1/_4$ bis $^1/_3$ Anteil Tyrosin mit nur geringen Mengen von Trijodthyroxin

e) Hormoninkretion durch Proteolyse des Thyreoglobulins durch eine Schilddrüsenprotease Thyroxin und Trijodthyronin verlassen in Aminosäureform die Schilddrüse

Nach neueren Forschungen kann als gesichert gelten dass die Schilddrüsenhormone einen direkten humoralen Angriffspunkt an jeder einzelnen Zelle haben Um welchen Wirkungsmechanismus es sich bei der Beeinflussung des Stoffwechsels handelt ist bis heute nicht *geklärt* Die Hormonwirkung lässt sich nach Lipner et al (1952) und Tabachnick et al. (1954) nicht an einen bestimmten Ort der Körperzelle festlegen Man hat jedoch den Eindruck als wenn den Mitochondrien in diesem Zusammenhang eine wesentliche Bedeutung zukommt Die gleichen Autoren weisen jedoch darauf hin dass das Thyroxin und das Trijodthyronin sich sehr unterschiedlich an verschiedenen Stellen der Zelle verhalten so im Kern in den Mitochondrien und Mikrosomen Unter dem Einfluss des Schilddrüsenhormons treten submikroskopische Veränderungen in Form von Mitochondrienquellungen unter Wasseraufnahme und Mitochondrienvermehrung in der Zelle auf Nach Hess und Brand (1964) werden dadurch intrazelluläre Enzymsysteme labilisiert und der Austausch im Stoffwechselmetabolismus zwischen den extra und intramitochondralen Reaktionsräumen ermöglicht Diese Aussage stellt nur *einen* Aspekt zur Wirkweise der Schilddrüsenhormone dar ganz sicherlich werden noch mehrere Faktoren im Spiele sein

Man kann den Einfluss der Schilddrüsenhormone auf die Zellbestandteile in eine Sofort und eine Spätwirkung aufgliedern. Die Sofortwirkung bei der Anwendung niedriger Hormonkonzentrationen beruht auf einer Steigerung von ATP-Synthese und Sauerstoffverbrauch mit einer Stimulierung der Eiweisssynthese Bei der Spätwirkung nach höheren Hormondosen (etwa 12 Std nach Hormongabe) erfolgt eine Anregung der Glykolyse und Induktion von Enzymsynthesen (Hess und Brand 1964) Die Änderung oder besser der Anstoss zur Enzymneubildung wird durch

eine hormonbedingte Substratänderung hervorgerufen. Pitt-Rivers und Tata (1959) beschrieben die Aktivitätsänderung von etwa 50 Fermenten unter dem Einfluss des Schilddrüsenhormons.

Erhöhte Fermentaktivitäten nach Hormongaben zeigten sich erwartungsgemäss bei den am Elektronentransport beteiligten Enzymen über die Atmungskette, aber auch andere Fermente liessen erhöhte Fermentaktivitäten unter dem Einfluss von Schilddrüsenhormonen erkennen (Dye und Waggener 1928 Markoff, 1935 Barker 1951 Maley 1957 Rawson et al. 1955 u. a.). Mit grosser Wahrscheinlichkeit liegt keine spezifische Wirkung des Schilddrüsenhormones auf irgendein Fermentsystem vor. Die unterschiedlichen Fermentaktivitäten – Aktivitäts- ab- oder zunahme – beruhen mutmasslich auf der veränderten chemischen Zusammensetzung von Körperflüssigkeiten und in der variablen Dynamik des Stoffwechsels. Man kann – wie schon betont – also lediglich Enzymwirkungen darstellen, jedoch in diesem Zusammenhang keine Angaben über den Wirkungsmechanismus der Enzyme machen. Versucht man eine einfache Formulierung zur Hormonwirkung zu geben, so darf man festhalten, dass die Schilddrüsenhormone auf den Stoffwechsel an der Stelle der oxydativen Phosphorylierung einwirken und die Bereitstellung von energiereichen Phosphaten steuern (s. auch Oberdisse und Klein, 1967).

Die Schilddrüsenhormone beeinflussen alle Stoffwechselbereiche. Im Eiweisshaushalt wirken physiologische Hormonmengen anabol, sie stimulieren die Eiweissynthese und den Eiweissabbau. Grosse Hormonkonzentrationen wirken katabol, woraus ein Phosphatverlust und eine negative Stickstoffbilanz resultieren kann. Durch Hormonmangel kommt es neben der Grundumsatzerniedrigung zu Eiweissansammlung in Interzellulärraumen bei verminderter Proteinsynthese (Crispell et al. 1956 Lewallen et al. 1959). Bei zunehmendem Hormonmangel steigen die Gesamtproteine im Plasma an, während der Gehalt an Mukoproteinen im Plasma abnimmt (Mustacchi et al. 1954).

Der Kohlenhydrathaushalt wird durch verschiedene Fermente gesteuert, die unter dem *Einfluss von Schilddrüsenhormonen* stehen. Spezifische Wirkungen dieser Fermente bei physiologischem Hormonspiegel sind nicht bekannt. Im Fettstoffwechsel ist bei Hormonmangel seit langem die Hypercholesterinämie bekannt (Epstein und Lande, 1922). Auf weitere Einzelheiten kann in diesem Zusammenhang nicht eingegangen werden. Durch den Hormonmangel wird eine Wasser- und Elektrolytretention bei Dehydration von Blut, Muskulatur und Gehirn bewirkt. Scholz et al. (1964) stellten dabei fest, dass extra- und intrazelluläre Verteilungsräume gleicher massen beteiligt sind. Durch Hormonzufuhr wird eine Diurese ausgelöst, die zu einer Vermehrung des Blutvolumens auf Kosten der Extrazellularflüssigkeit führt (Pitt-Rivers und Tata, 1959).

Die Grundsubstanz des Bindegewebes steht in besonderem Masse unter dem Einfluss des Schilddrüsenhormons. Iversen (1954) applizierte Meerschweinchen Thyreotropin, was zu einer Vermehrung von hyaluronidasesensitiven sauren Mucopolysacchariden in verschiedenen Bindegewebsbereichen führte. Auffällig war die Unterschiedlichkeit der Reaktion in verschiedenen Bindegewebsarealen, z. B. wird das retrobulbäre Gewebe besonders betroffen (Asboe-Hansen und Iversen 1951 Iversen und Asboe-Hansen 1952). Mit grosser Wahrscheinlichkeit wird der Exophthalmus durch das hohe Wasserbindungsvermögen der Hyaluronsäure, welches eine oedematöse Aufquellung des Gewebes verursacht, hervorgerufen. Nach Ludwig et al. (1950) findet man in dem betroffenen Gewebe des retrobulbären Raumes eine erhebliche Steigerung der Metachromotropie. Das prätibiale Oedem des hypothyreotischen Patienten ist gekennzeichnet durch eine Vermehrung der Grundsubstanz, in der eine starke Zunahme von sauren Mukopolysacchariden beobachtet werden kann. Diese sauren MPS

sind partiell hyaluronidasesensitiv perjodat reaktiv metachromotrop und zeigen eine positive Eisenbindungsreaktion (Asboe Hansen *1950c* Palitz und Brunner 1950 Follis *1950* Brewer *1951* Campani und Pelloja *1951*) Nach Gaben von Schilddrüsenhormonen nimmt der Gehalt an sauren Mukopoly sacchariden stark ab

Meyer und Chaffée (1941) Ludwig et al (1950) sowie Brewer (1951) führen das erhebliche Wasserbindungsvermögen im myxomatösen Gewebe auf den hohen Gehalt an Hyaluronsäuren zurück während sie die Chondroitin Schwefelsäure für die Alteration an den Bindegewebsfibrillen verantwortlich machen Das ausgeprägte Wasserbindungsvermögen des Mukopolysaccharid Proteinkomplexes beruht nach Bull (1951) auf der Anwesenheit von polaren Gruppen Bei längerem Bestehen des Myxoedems nimmt der Gehalt an Hyaluronsäure im Gewebe ab während die Chondroitin-Schwefelsäure zunimmt Darüberhinaus ist neben der quantitativen Veränderung der Mukopolysaccharide auch die Relation zwischen Hyaluronsäure und Chondroitinsulfatgehalt verschoben Während normalerweise im Bindegewebe auf 100 g Gewebe 25 mg Hyaluronsäure und 26 mg Chondroitin sulfat kommen findet sich beim lokalen Myxoedem ein Verhältnis von 64–270 mg Hyaluronsäure 49–160 mg Chondroitin-Sulfat Offensichtlich liegt das Phänomen darin begründet dass die freie Grundsubstanz welche normalerweise zu einem grossen Teil aus Hyaluronsäure besteht beim Myxoedem bevorzugt betroffen wird (Watson und Pearce 1947 1949 1950)

Del Conte et al (1955) hatten bei Ratten nach Thyreoidektomie und Anwendung thyreostatischer Substanzen eine Vermehrung von sauren MPS im Hautbindegewebe festgestellt Sie fanden jedoch keine direkte Beziehung zwischen der Vermehrung der sauren MPS und der Zahl der Mastzellen Asboe Hansen (1950*c*) jedoch hält nach seinen Untersuchungsergebnissen eine Beziehung zwischen den vermehrten sauren MPS und der Zahl der Mastzellen für sehr wahrscheinlich Die Mastzellen im Bindegewebe gehen beim Myxoedem starke Veränderungen ein. Sie weisen eine metachromatische Granulierung auf die sich unter dem Einfluss von Schilddrüsenhormonen zurückbildet Dieser Befund dürfte im Zusammenhang mit der Produktion saurer Mukopolysaccharide (Hyaluronsäure) durch die Mastzellen stehen eine Vorstellung, die besonders von Asboe Hansen (1950*a b c* 1954) propagiert wird Dafür spricht u a dass die Mastzellen und die Hyaluronsäure in den gleichen Bindegewebsprovinzen vorkommen um die Mastzellen sich häufig extrazellulär metachromotropes Material findet nach enzymatischem Abbau der Grundsubstanz eine Einwanderung von Mastzellen und deren Degranulierung beobachtet werden kann

Parallel zur Vermehrung der sauren Mukopolysaccharide im myxomatös veränderten Bindegewebe geht eine Erhöhung der Mukopolysaccharide im Serum (Mancini et al 1952)

Nicht alle Zusammenhänge zwischen Schilddrüsenhormonen und Bindegewebe sind bislang aufgeklärt worden Möglicherweise werden auch noch andere Mukopolysaccharide als die erwähnte Hyaluronsäure und das Chondroitinsulfat beteiligt worauf Brewer (1951) Farvilli (195?) sowie Keining und Braun-Falco (1956) hinwiesen

Asboe Hansen (1950*c*) nimmt an dass das Schilddrüsenhormon über seine stimulierende und hemmende Wirkung auf die thyreotrope Aktivitä der Hypophyse die Verteilung und Produktion der sauren MPS regelt d h die Vermehrung der sauren MPS beim Myxoedem als Folge der Überschussproduktion am thyreotropen Hormon zu erklären sind Angriffspunkt sollen nach Asboe Hansen die perivasculären Mastzellen sein

8 Einteilung der Hypothyreosen, klinische Symptomatik

Die Hypothyreosen *lassen sich in primäre* und *sekundäre Erkrankungen* einteilen. Im folgenden wird die Aufgliederung nach Scazziga und Lemarchand-Béraud (1966) zugrunde gelegt

I Primäre Hypothyreose

a) *Hypothyreose* infolge quantitativ gestörter Hormonbildung
   - aa) Hypothyreose infolge Fehlens oder Verminderung des funktionierenden *Schilddrüsengewebes*
   - bb) Idiopathische Hypothyreose des Kindes *und* des *Erwachsenen*

b) Hypothyreose infolge qualitativer Störung der Hormonsynthese
   - aa) Erworbene Störungen der Hormonsynthese aus exogenen oder *endogenen* Gründen
   - bb) Kongenitale Störung der Hormonsynthese

II Sekundäre Hypothyreose

a) Sekundäre Hypothyreose bei Läsionen im ZNS

b) Sekundäre Hypothyreosen infolge Jodmangels

Aus der Vielzahl der Ursachen für eine verminderte oder aufgehobene Funktion der Schilddrüse soll die primäre Hypothyreose herausgegriffen werden, da sie am ehesten den durchgeführten experimentellen Untersuchungen entspricht. Noch weiter einschränkend wird besonders die Form der Hypothyreose besprochen, die im Erwachsenenalter auftritt *und auf einer quantitativen* Störung der Hormonproduktion beruht. *Sie kann durch mangelhaft* angelegtes Schilddrüsengewebe entstehen oder aber Folge einer zu radikalen Strumektomie sein. Zum anderen lässt sie sich auf eine *Thyreoiditis* (z. B. Hashimotothyreoiditis) oder einen malignen Schilddrüsentumor zurückführen.

Die Hypothyreose kommt in verschiedenen Stärkegraden vor, was sich klinisch in einer manchmal nur diskreten Symptomatik, in anderen Fällen im *voll ausgeprägten* Krankheitsbild des Myxoedems äussert. Der Grad der mangelhaften Hormonproduktion lässt sich durch die Bestimmung des proteingebundenen Serumjods festhalten, wobei Werte zu *meist unter 4,5 µg/100 ml vorliegen. Weitere* diagnostische Massnahmen wie Messung des Radiojodumsatzes, Stimulierung der Schilddrüse mit thyreotropem Hormon und Szintigraphie sollen nur am Rande erwähnt werden.

Bei starker *Unterfunktion der Schilddrüse* liegt häufig ein Myxoedem der Haut mit Prädilektionsstellen im prätibialen Bereich des Unterschenkels vor. Die Patienten zeigen eine abnorme Ermüdbarkeit und Apathie, es stellen sich Störungen der *Merkfähigkeit*, der Konzentration und des Antriebes ein. Sehr typisch ist eine hartnäckige Obstipation. Bei der nur leichten *Form der Schilddrüsenunterfunktion* kann die Diagnostik Schwierigkeiten bereiten, *da sich typische Symptome nur diskret* äussern und häufig genug Anlass zu *Fehlinterpretationen des Krankheitsbildes ergeben*. Weitere *Einzelheiten der Symptomatik* und *Diagnostik der Schilddrüsenunterfunktion* lassen sich den ausführlichen Darstellungen *von Oberdisse und Klein (1967), König (1968), Klein (1969) u. a.* entnehmen.

sind partiell hyaluronidasesensitiv perjodat reaktiv metachromotrop und zeigen eine positive Eisenbindungsreaktion (Asboe-Hansen 1950*c* Palitz und Brunner 1950 Folbs 1950 Brewer 1951 Campani und Pelloja 1951) Nach Gaben von Schilddrüsenhormonen nimmt der Gehalt an sauren Mukopoly saccharиden stark ab

Meyer und Chaffée (1941) Ludwig et al (1950) sowie Brewer (1951) führen das erhebliche Wasserbindungsvermögen im myxomatösen Gewebe auf den hohen Gehalt an Hyaluronsäuren zurück während sie die Chondroitin-Schwefelsäure für die Alteration an den Bindegewebsfibrillen verantwortlich machen Das ausgeprägte Wasserbindungsvermögen des Mukopolysaccharid Proteinkomplexes beruht nach Bull (1951) auf der Anwesenheit von polaren Gruppen Bei längerem Bestehen des Myxoedems nimmt der Gehalt an Hyaluronsäure im Gewebe ab während die Chondroitin Schwefelsäure zunimmt Darüberhinaus ist neben der quantitativen Veränderung der Mukopolysaccharide auch die Relation zwischen Hyaluronsäure und Chondroitinsulfatgehalt verschoben Während normalerweise im Bindegewebe auf 100 g Gewebe 25 mg Hyaluronsäure und 26 mg Chondroitin sulfat kommen findet sich beim lokalen Myxoedem ein Verhältnis von 64–270 mg Hyaluronsäure 49–160 mg Chondroitin-Sulfat Offensichtlich liegt das Phänomen dann begründet dass die freie Grundsubstanz welche normalerweise zu einem grossen Teil aus Hyaluronsäure besteht beim Myxoedem bevorzugt betroffen wird (Watson und Pearce 1947 1949 1950)

Del Conte et al (1955) hatten bei Ratten nach Thyreoidektomie und Anwendung thyreostatischer Substanzen eine Vermehrung von sauren MPS im Hautbindegewebe festgestellt Sie fanden jedoch keine direkte Beziehung zwischen der Vermehrung der sauren MPS und der Zahl der Mastzellen Asboe Hansen (1950*c*) jedoch hält nach seinen Untersuchungsergebnissen eine Beziehung zwischen den vermehrten sauren MPS und der Zahl der Mastzellen für sehr wahrscheinlich *Die Mastzellen* im Bindegewebe gehen beim Myxoedem starke Veränderungen ein Sie weisen eine metachromatische Granulierung auf die sich unter dem Einfluss von Schilddrüsenhormonen zurückbildet Dieser Befund dürfte im Zusammenhang mit der Produktion saurer Mukopolysaccharide (Hyaluronsäure) durch die Mastzellen *stehen eine* Vorstellung die besonders von Asboe Hansen (1950*a b c* 1954) propagiert wird Dafür spricht u a dass die Mastzellen und die Hyaluronsäure in den gleichen Bindegewebsprovinzen vorkommen um die Mastzellen sich häufig extrazellulär metachromotropes Material findet nach enzymatischem Abbau der Grundsubstanz eine Einwanderung von Mastzellen und deren Degranulierung beobachtet werden kann

Parallel zur Vermehrung der sauren Mukopolysaccharide im myxomatös veränderten Bindegewebe geht eine Erhöhung der Mukopolysaccharide im Serum (Mancini et al 1952)

Nicht alle Zusammenhänge zwischen Schilddrüsenhormonen und Bindegewebe sind bislang aufgeklärt worden Möglicherweise werden auch noch andere Mukopolysaccharide als die erwähnte Hyaluronsäure und das Chondroitinsulfat beteiligt worauf Brewer (1951) Farvilli (195?) sowie Keining und Braun-Falco (1956) hinwiesen

Asboe Hansen (1950*c*) nimmt an dass das Schilddrüsenhormon über seine stimulierende und hemmende Wirkung auf die thyreotrope Aktivität der Hypophyse die Verteilung und Produktion der sauren MPS regelt d h die Vermehrung der sauren MPS beim Myxoedem als Folge der Überschussproduktion am thyreotropen Hormon zu erklären sind Angriffspunkt sollen nach Asboe Hansen die perivasculären Mastzellen sein

10 Besprechung der Ergebnisse

Gehörstörungen als Begleitsymptom von Schilddrüsenfunktionen im Sinne einer Hypothyreose kommen überwiegend bei drei Erkrankungen vor, die kurz noch einmal angeführt werden sollen:

1. Der endemische Kretinismus
2. Das sog. Pendred-Syndrom.
3. Die primäre Hypothyreose infolge quantitativ und qualitativ gestörter Hormonbildung.

Die beiden ersten Formen der endemische Kretinismus und das sog. Pendred-Syndrom in Verbindung mit Hörstörungen können hinsichtlich der Genese der Innenohrstörung nur Gegenstand von Denkmodellen sein, da es wohl kaum oder nur sehr schwer gelingen wird, entsprechende experimentelle Untersuchungen anzustellen. Die von früheren Autoren aufgezeigten pathologisch-anatomischen Substrate des Innenohres beim endemischen Kretin deuten in ihrer Gesamtheit am ebesten auf Missbildungen hin, andererseits kann man sich des Eindruckes nicht erwehren, dass manche der beschriebenen Veränderungen, insbesondere die im Innenohr gelegenen, post mortal entstanden und Folge fortschreitender Autolyse sind, ein Einwurf, der auch von früheren Autoren gemacht wurde. Gerade die morphologischen Innenohrbestandteile sind in einem besonderen Ausmass gegen post mortale Veränderungen empfindlich. Nicht selten kann man beim Tierkadaver (Meerschweinchen) schon nach 24-48 Std. kein Cortiorgan mehr nachweisen.

Die Ergebnisse der pathologisch-anatomischen Untersuchungen müssen auch schon deswegen enttäuschen, als sie in den meisten Fällen die schwere Schallempfindungsstörung nicht erklären können. Zum anderen muss man die technischen Möglichkeiten zur Schnitthersteilung mit langdauernden Entkalkungsprozessen in Rechnung stellen, wodurch das morphologische Substrat in einem Ausmasse alteriert wird, welches Rückschlüsse auf eine mögliche Funktionsbeeinträchtigung, basierend auf einer Schädigung des Schallperzeptionsapparates, gar nicht mehr zulässt. Ein letztes wichtiges Argument gegen die Aussagekraft der erhobenen Befunde ist die Tatsache, dass endemischer Kretinismus und schwere Hörstörungen bzw. Taubstummheit nebeneinander ohne direkten Zusammenhang vorkommen können – wie es besonders von Schweizer Autoren betont wurde – dass also im vorliegenden Falle patho-morphologische Veränderungen im Innenohr der Schilddrüsendysfunktion zugeordnet werden, deren Verantwortlichkeit für die erhobenen Befunde zumindest in Zweifel gezogen werden kann.

Experimentelle Untersuchungen über die Beeinflussung des Innenohres durch die Hypothyreose lassen sich nur durch Verminderung oder totale Entfernung von Schilddrüsengewebe anstellen, sei es durch operative Entfernung der Schilddrüse, wie in den vorliegenden Experimenten ausgeführt, oder aber durch Blockierung des Jodeinbaus zu Monojodtyrosin mittels Thiouracil (Ritter und Lawrence 1960; de Vos 1963; Ritter 1967). Das Versuchsmodell würde danach vergleichbar sein mit der primären Hypothyreose infolge Mangel an Schilddrüsenhormonen, eine Erkrankung, die elektroakustisch nachweisbare Hörverluste häufig über das ganze Tonfrequenzband hin erzeugt.

Die mikromorphologische Untersuchung des Innenohres beim Meerschweinchen unter Mangel an Schilddrüsenhormonen gestaltet sich insofern überaus schwierig, als die zu erwartenden und auch überraschenden Ergebnisse in ihrer Deutung auf die komplexe Wirkungsweise der Hormone abgestimmt werden müssen, d. h. die vielfältigen Angriffspunkte des Thyroxins werden eine Vielzahl von Veränderungen in den einzelnen Innenohrstruk-

9 Experimentelle Arbeiten zum Einfluss der Schilddrüsenhormone auf das Gehörorgan (aus der Literatur)

Nach Durchsicht der otologischen Literatur liegen nur wenige experimentelle Arbeiten zur Entstehungsursache der hypothyreotisch bedingten Schwerhörigkeit vor. So finden sich Arbeiten von Poulsen (1959), Ritter und Lawrence (1960), de Vos (1963) sowie Ritter (1967).

Poulsen (1959) untersuchte die Innenohrstrukturen von thyreoidektomierten Meerschweinchen mit histologisch-histochemischen Methoden und stellte dabei vermehrte Ansammlungen von Hyaluronsäure im Endo- und Perilymphraum fest. Zum anderen beobachtete er eine Vermehrung von Mastzellen in den entsprechenden Strukturen. Der Autor diskutiert aufgrund seiner Beobachtungen und Untersuchungsbefunde die Möglichkeiten der Entstehung einer Schwerhörigkeit im Ablauf einer Hypothyreose.

Ritter (1967) verwendete für seine Untersuchungen Hühnchenembryonen, denen er am 4., 9. und 14. Tag nach Beginn der Bebrütung 2 mg Thiouracil injizierte. Nach Ausschlüpfen der Tiere, die sofort getötet wurden, zeigten sich bei den Hühnchen, die am 9. und 14. Tag Thiouracil erhielten, keine auffälligen Veränderungen im Bereich der akustischen Papille. Erst die am 4. Tag nach Beginn der Bebrütung injizierten Tiere liessen nach Ansicht des Autors Alterationen erkennen, die auf Mangel an funktionierendem Schilddrüsengewebe zurückgeführt wurden. Die Tiere schlüpften etwas verspätet aus dem Ei, hatten unterentwickelte Flügel, der Dottersack war unvollständig resorbiert. Die Hauptveränderungen lagen im Bereich des Innenohres (akustische Papille), während im Mittelohr lediglich eine Verknöcherungsstörung des Steigbügels nachweisbar war. Im Innenohr zeigte die Tectorialmembran einen Kontakt mit den Haarzellen, diese jedoch waren zahnförmig deformiert und von den Nervenfasern durch ein deutliches Oedem im Zwischengewebe getrennt. Die angeführten Veränderungen fanden sich bei allen untersuchten Hühnchen, die während der Inkubation am 4. Tag 2 mg Thiouracil erhalten hatten.

De Vos (1963) verabreichte weissen Mäusen, weissen Ratten und Hamstern Propylthio-Uracil (5%ige wässerige Lösung) über 6–21 Wochen. Danach wurden die Tiere getötet und die Felsenbeine nach Fixierung und Entkalkung in Celloidin und Paraffin eingebettet und mit Hämatoxilin-Eosin gefärbt. Die morphologische Alteration des Innenohres, welche sich nach Ansicht des Autors nach 7-wöchiger Thiouracilbehandlung einstellte, wurde als leichte bis mittelschwere Degeneration der Spiralganglien beschrieben. Leichte degenerative Zeichen bemerkte de Vos auch am N. acusticus. Darüberhinaus beobachtete er eine Verdickung der Basilarmembran. Der Autor betont die Verschiedenartigkeit zwischen den Gehörstörungen beim Kretinismus, beim Pendred-Syndrom und bei der Schwerhörigkeit infolge einer im späteren Lebensalter erworbenen Hypothyreose. Er stimmt der Hypothese von Trotter (1960) zu, dass möglicherweise der Schilddrüsenmangel keine entscheidende Rolle für die Hörstörung spielt, sondern eine schädliche im Blut zirkulierende Substanz, die Enzymstörungen im Hörorgan und in den zentralen Schaltstellen verursacht, dafür verantwortlich ist.

Schliesslich begannen Schätzle und Haubrich (1967) eine differenzierte histomorphologische Bearbeitung der Innenohrstrukturen bei der experimentellen Hypothyreose des Meerschweinchens.

wechsel der äusseren Haarzellen fest erst später machten sich Veränderungen an den inneren Haarzellen bemerkbar. Die verschiedenartige Empfindlichkeit der äusseren und inneren Haarzellen kann als Beweis für die Duplizitätstheorie des Hörens herangezogen werden, die von Meyer zum Gottesberge (1948) formuliert wurde. Danach kommt den verschiedenen Sinneszellen im Cortiorgan eine unterschiedliche Funktion hinsichtlich der Hörschwelle und der Frequenzanalyse zu.

Berücksichtigt man zunächst die experimentellen Ergebnisse zur quantitativen und qualitativen Verteilung der Fermente in den Innenohrstrukturen unter Mangel an Schilddrüsenhormonen, so darf man vorausschicken, dass die Änderung der Enzymaktivität an den einzelnen Orten des Innenohres relativ diskret ist, sich aber bei genauer mikroskopischer Exploration der histochemischen Schnitte deutlich abzeichnet. Insbesondere fällt die Abnahme der Enzymaktivität bei der Esterase- und Glukosaminidasereaktion auf. In Übereinstimmung mit anderen Autoren dokumentiert sich die quantitative Änderung des Fermentgehaltes überwiegend in den äusseren Haarzellen und nicht zuletzt in der Stria vascularis und im Ganglion spirale. Bei manchen Glykosidasen (Galaktosidase und Glukuronidase) kann keine eindrucksvolle Änderung der Enzymkonzentration dokumentiert werden, während die N-Azetyl-Glukosaminidase in den äusseren Haarzellen, in der Stria vascularis und im Ganglion spirale erheblich abnimmt. Die Sulfatase-Reaktion ist unverändert kräftig. Eine ähnliche Situation liegt auch im Saccus endolymphaticus vor, dessen aktive Zone der Pars intermedia eine sehr auffällige Reduzierung von Enzymaktivitäten der unspezifischen Esterase und der Glukosaminidase erkennen lässt.

Zur Deutung der angeführten Fermentbefunde lassen sich verschiedene Gesichtspunkte anführen, deren Wertigkeit im einzelnen nur abgeschätzt, im Gesamtbild jedoch recht einheitlich beurteilt werden kann.

Wie Hess und Brand (1964) formulierten, kommt es durch Zufuhr von Schilddrüsenhormonen zu einer intrazellulären Labilisierung von Multienzymsystemen mit vermehrtem extra- und intrazellulären Stoffaustausch. Durch Substratänderung infolge einer Hypo- oder Hyperthyreose wird eine Induktion von verschiedenen Fermenten bedingt, die sich im Ansteigen oder Abfallen von Enzymaktivität äussern kann. Als Beispiel mag das Verhalten der Galaktosidase, der Glukuronidase und der Sulfatase dienen. Alle diese Fermente spielen mit einer hohen Wahrscheinlichkeit eine wichtige Rolle im Stoffwechsel der Gluko-Mukoproteide und sauren Mukosubstanzen, deren Abbau sie an bestimmten Bindungen vollziehen. Es kann keinen Zweifel darüber geben, dass infolge der Hypothyreose durch vermehrte, histochemisch manchmal nicht zu erfassende Ablagerungen von Mukosubstanzen eine Adaptation der Fermentaktivität an das veränderte Substrat, z. B. der Bindegewebsgrundsubstanz, vonstatten geht, die sich in einer Aufrechterhaltung eines bestimmten Enzymstatus oder sogar Vermehrung äussern kann. In besonderem Masse scheint der Aryl-Sulfatase eine Bedeutung für den cochlearen Stoffwechsel sulfatierter Glukoproteide und Mukopolysaccharide zuzukommen. So findet sich auch dieses Ferment bei der Hypothyreose in einer starken Aktivität. Auffällig bleibt jedoch die Abnahme der N-Azetyl-Glukosaminidase, deren grosse Bedeutung für die Aufschlüsselung der sauren Mukopolysaccharide mit deren Hauptbestandteil N-Azetyl-Glukosamin bekannt ist.

Von gleichem Interesse erscheint auch die hohe Enzymaktivität der Sulfatase an Orten des Innenohres, die eine Bedeutung für die Sekretion und Resorption der Peri- und Endolymphe haben, wie die Stria vascularis, Sulcus spiralis externus, Plexus cochlearis mit dem Tractus spiralis arteriosus et venosus, Saccus endolymphaticus u. a. Vergleiche von Enzymkonzentrationen an verschiedenen *Bereichen der Cochlea* und des Saccus endolymphaticus mit den autoradiographisch gemessenen Eiweissumsätzen an den entspre-

turen bedingen deren morphologische Darstellbarkeit auf Schwierigkeiten stossen kann.

Der ungestörte oxydative Stoffwechsel ist eine Hauptvoraussetzung für eine normale Haarzellfunktion was von Misrahy et al (1958) besonders hervorgehoben wurde Tritt ein Mangel an Sauerstoff ein werden sich die Haarzellen auf Grund ihres hohen Gehaltes an Lactatdehydrogenase (Vosteen 1961 1964) über die anaerobe Glykolyse für eine kurze Zeit einen ausreichenden Zellstoffwechsel sichern Der Stria vascularis hingegen fehlt weitgehend diese Fermentausstattung so dass sie schon recht frühzeitig unter einer Hypoxydose geschädigt wird Neben der LDH wies Vosteen auch Glutamatdehydrogenase und Alpha-Glyzero-Phosphatdehydrogenase nach deren Verbreitung im Innenohr weitgehend der der LDH entspricht Im Gegensatz zu diesen Ergebnissen fanden Spoendlin und Balogh (1963*a* *b*) die LDH fast ausschliesslich in den äusseren Haarzellen und hier in schwankender Aktivität Bei der Hypothyreose kann als ziemlich sicher gelten dass die oxydative Phosphorylierung in ihrem Fermentspektrum als Angriffspunkt des Schilddrüsenhormons gestört und die Reservestellung von energiereichen Phosphaten vermindert wird Da die Haarzellen insgesamt bei einer Reduzierung oxydativer Stoffwechselvorgänge sehr empfindlich reagieren liesse sich dadurch die oftmals zu beobachtende Beeinträchtigung aller Tonfrequenzen d h die Funktionsherabsetzung aller Haarzellen erklären Die Haarzellen der Basalwindung sind ohnehin aufgrund ihrer höheren Belastung empfindlicher als die Hörzellen der anderen Windungen was sich im Audiogramm durch einen stärkeren Hörverlust im Hochtonbereich dokumentieren wird Mutmasslich durfte der Grad der hypothyreotischen Stoffwechsellage einen Einfluss auf die Funktionsbeeinträchtigung der Haarzellen haben was aber von manchen Autoren bestritten wird (de Vos 1963 Post 1964) Diese Autoren fanden Patienten mit relativ leichter Hypothyreose und stärkerer Hörstörung andere Kranke litten an einem voll ausgeprägten Myxoedem ohne dass eine Schwerhörigkeit nachweisbar war Dieser Befund erscheint insofern bemerkenswert als die Herabsetzung der oxydativen Phosphorylierung infolge Mangels an Schilddrüsenhormonen in ihrer graduellen Abstufung kein alleiniges Kriterium für das Ausmass der Innenohrstörung sein kann Man muss von der Überlegung ausgehen dass die Ursache der Innenohrstörung rein anatomisch gesehen an verschiedenen Stellen der Cochlea lokalisiert sein kann 1 an den Haarzellen 2 am N acusticus mit seinen präganglionären und postganglionären Fasern und 3 am sezernierenden und resorbierenden System des gesamten Ductus cochlearis (z.B Stria vascularis Limbus spiralis Prominentia spiralis u a) und des Ductus sowie Saccus endolymphaticus Daraus liessen sich Schlüsse über mögliche Störungen der Elektrolytverhältnisse in Endo- und Perilymphe ableiten

Am leichtesten lassen sich die hin und wieder relativ selten auftretenden Schalleitungsstörungen beim Myxoedem erklären da hier durch eine erhebliche Schwellung der Mittelohrschleimhaut und eine sich daraus ergebende gewisse Versteifung der Gehörknöchelchen eine Schwingungsbeeinträchtigung des schallübertragenden Apparates verursacht wird Diesen Befund konnten wir an einigen Tieren beobachten

Die äusseren und inneren Haarzellen besitzen aufgrund histologischer histochemischer und elektrophysiologischer Untersuchungen eine sehr unterschiedliche Anfälligkeit gegenüber schädlichen Einwirkungen Rüedi (1951) beobachtete bei Streptomycingaben und Beschallung in Tierversuchen zunächst eine Schädigung der äusseren Haarzellen erst später traten Läsionen der inneren Haarzellen hinzu Vosteen (1958) wies nach funktioneller Belastung zunächst eine Fermentabnahme in den äusseren Haarzellen nach Beck (1959) stellte bei Reintonbeschallung reversible Zellkernveränderungen und eine Störung im Eiweiss und RNS Stoff

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chenden Strukturanteilen zeigen deutlich eine Übereinstimmung von Fermentaktivität und Höhe des Eiweissumsatzes (Plester 1960 Meyer zum Gottesberge und Plester 1961 Koburg und Plester 1962*a* *b* Balogh und Koburg 1965) Die Inkorporationsraten von H_3 Leucin H_3-Tyrosin und H_3-Phenyl Ala nin ergaben beträchtliche Werte für die Stria vascularis was sich in der chromophilen endolymphnahen und weniger in der chromophoben Schicht abzeichnete (Koburg und Plester 1962*a*)

Entsprechende Befunde zeigten sich am Saccus endolymphaticus dessen hoher Ge halt an Sulfatase im gesamten Epithelbereich und vorzugsweise in der Pars intermedia von Schätzle und Haubrich (1966) und hoher Ei weissumsatz mit H_3 Phenyl Alanin autoradiographisch von Haubrich und Koburg (1966) sowie Koburg et al (1967) nachgewiesen wurde

Als Parallelbefund mag der hohe Gehalt der Stria vascularis an sog freien Sulfhydrylen dienen die von Rauch (1964) als möglicher Beweis für die Anwesenheit SH abhängiger Fermente (Carboanhydrase Esterase) ange führt wurden Auch unter hypothyreotischen Bedingungen nimmt der Gehalt von Sulfhydry len nicht ab

Infolge der Schilddrüsenunterfunktion er wartet man eine verminderte Proteinsynthese mit vermehrter Eiweissansammlung im Inter zellularraum (Crispell et al 1957 Rothschild et al 1957 Lewallen et al 1959) Soweit man die Befunde am Innenohr des Meer schweinchens deuten kann darf man vielleicht annehmen dass eine ausreichende Proteinsyn these zumindest fur die infolge Substratande rungen induzierten Fermente trotz Schild drüsenunterfunktion gewährleistet wird

Dass PAS positive eosinophile nicht saure und nicht hyaluronidasesensible Material welches sich bei einigen Tieren im Bereich des Modiolus nachweisen lässt kann als ex trazellulär gelagertes Glukoproteid (=Fibri noid) gedeutet werden Ob für die Auswande rung der grossmolekularen Peptide und Proteine eine durch die Hypothyreose bedingte hypoxische Wandschädigung der Gefässe ver antwortlich gemacht werden kann soll nur am Rande diskutiert werden

Eine weitere Struktur des Innenohres, der N acusticus ist gleichfalls von einer ungestörten Proteinsynthese abhängig. Weiss und Hiscoe (1948) stellten die Theorie des axona len Stofftransportes von der Ganglienzelle in das zugehörige Axon auf Man hat sich dar unter eine Zytoplasmawanderung aus dem Perikaryon der Ganglienzelle in das Axon vorzustellen Diese Untersuchungen wurden im einzelnen von Koenig (1958) Friede (1959) Droz und Leblond (1963) Lux et al (1970*a* *b*) am peripheren und zentralen Nerven histochemisch und autoradiographisch durchge führt Haubrich und Koburg (1967) stellten eine beträchtliche Eiweissmigration im N acusticus nach zentral und peripher mit Hilfe der Messung von Inkorporationsraten be stimmter tritiummarkierter Aminosäuren (H_3-Tyrosin H_3-Phenyl Alanin H_3-Leucin) in verschiedenen Zeitabständen nach der Injek tion fest Ohne Zweifel ist eine intakte Reiz leitung im Nerven vom ungestörten Flow von Zytoplasmaanteilen aus der Ganglienzelle in das Axon abhängig Im folgenden wird noch ersichtlich werden inwiefern die Voraussetzung des intakten ,axonal flow aufgrund der hypothyreotischen Stoffwech sellage durchbrochen und hiermit ein Aspekt zur Aufklärung der resultierenden Innenohr störung dargelegt werden kann Damit zu sammenhängend kommt auch der Abnahme der N Azetyl-Glukosaminidase in den Spiral ganglienzellen bei der Hypothyreose als Aus druck der verminderten Proteinsynthese eine Bedeutung zu Das im Stoffwechsel der Muko- und Glukosubstanzen eine dominierende Rol le spielende Ferment wird normalerweise in hoher Konzentration in den Ganglienzellen angetroffen

Die von de Vos (1963) erhobenen Befunde bei hypothyreotischen Nagern in Form von degenerativen Veränderungen an den Zellen des Ganglion spirale liessen sich durch die

histochemischen Befunde nicht verifizieren. Da jedoch die Schnitte von de Vos überwiegend nur mit Hämatoxylin-Eosin gefärbt wurden, muss man das Ergebnis mit Zurückhaltung beurteilen, zumal die sog. degenerativen Veränderungen eine weite Palette pathomorphologischen Substrates mit einer gewissen Unverbindlichkeit in der Aussagekraft umspannen.

Ein weiteres sehr eindrucksvolles Ergebnis zeichnet sich bei der Darstellung der Gluko-Mukoproteide und sauren Mukosubstanzen beim hypothyreotischen Meerschweinchen ab. Wie im experimentellen Teil der Arbeit ausführlich dargestellt, findet sich in den verschiedenen Skalen und in der Umgebung des *N. acusticus* sowie des Plexus cochlearis teilweise perjodatreaktives, teilweise hyaluronidaseresistives metachromotropes Material, welches bei Kontrolltieren nicht beobachtet werden kann. Auch im Saccus endolymphaticus fällt eine alcianophile hyaluronidaseempfindliche Substanz auf, während normalerweise dort ein nur PAS-positives Material aufgefunden wird (Mukoproteide). Beim Kontrolltier sind im Gegensatz zu den hypothyreotischen *Tieren die Skalen* optisch leer, was jedoch kein Beweis für die Anwesenheit oder Abwesenheit von sauren Mukosubstanzen in den *Innenohrflüssigkeiten* darstellt. Die Nichtfärbbarkeit der Endo- und Perilymphe ergibt lediglich einen Hinweis für nur sehr geringe Mengen der beschriebenen Substanzen.

Um die Bedeutung der sauren Mukopolysaccharide für den Hörvorgang zu verstehen, muss kurz auf wesentliche Arbeiten *zu diesem* Thema zurückgegriffen werden. Békésy nahm eine biologische Stromquelle in der Scala media an, die die hohe Potentialdifferenz zwischen der positiven Endolymphe und dem negativen Potential der Haarzellen aufrecht *erhielt*. Biochemisch konnten Vilstrup und Jensen (1954) hyaluronidaseсensible saure MPS in der Endolymphe von Selachiern ausmachen, was hingegen in der Perilymphe nicht gelang. Jensen, Koefoe und Vilstrup (1954) machten Modellversuche, indem sie eine Kaliumhyaluronatlösung in einem Glasrohr mit folgendem Ergebnis bewegten. Wurde die hyaluronhaltige Flüssigkeit in Bewegung gesetzt, so entstand in der Bewegungsrichtung ein positives, am anderen Ende der Flüssigkeitssäule ein negatives Potential (Displacements potentials). Diese Verschiebepotentiale wurden von Christiansen, Jensen und Vilstrup (1961) sowie Christiansen (1962) als Biegungspotentiale fadenartiger Polyelektrolyte gedeutet. Dohlmann (1960) bezieht gleichfalls die Mukopolysaccharide als wichtiges Substrat für die Schalltransformation im Bereich der Cochlea mit ein. Der Autor stellte fest, dass die grössten Potentialänderungen in der unmittelbaren Umgebung der Sinneshaare zu finden waren. Durch eine Absorbierung von Hyaluronatmolekülen an den Haaren wird bei der Verschiebung derselben infolge eines adäquaten Reizes in Gegenwart der Kaliumionen in der Endolymphe ein Verschiebepotential ausgelöst. Dabei ist *zu* beachten, dass die durch die Sinneshaare bewirkte erhebliche Oberflächenvergrösserung der Haarzelle eine Zellmembran darstellt, die nicht für Elektrolyte durchgängig ist. Sie bildet nach Dohlmann eine dielektrische Schicht, so dass ihr bei der grossen endolymphwärts gerichteten Fläche eine Kondensatorwirkung zukommt.

Citron und Exley (1957) fanden bei Meerschweinchen in der Peri- und *Endolymphe* Hexosamin in geringen Mengen (5–8 mg%). Schneider und Schindler (1968) wiesen biochemisch N-Azetyl-Glukosamin in *niedriger* Konzentration in der Peri- und Endolymphe nach. Ishiyama (1969) konnte durch Dünnschichtchromatographie geringe Mengen von sauren Mukosubstanzen in den Innenohrflüssigkeiten isolieren (weniger als 3 mg/100 ml).

Letztlich sei *noch auf die* Ionenverhältnisse *in der Endo- und Perilymphe* hingewiesen. Die Endolymphe stellt in ihrer Zusammensetzung eine kaliumreiche extrazelluläre Flüssigkeit dar, während die Perilymphe eine hohe Konzentration von Natrium aufweist (Davis *et al.* 1958, 1959; Rauch, 1964 u. a.). Die

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Die vermehrte Ansammlung von Hyaluronsäure-Molekülen in den Innenohrflüssigkeiten hat gleichfalls einen Einfluss auf die *cochleare Osmoregulation insofern* als die Hyaluronsäure aufgrund ihrer zahlreichen polaren Gruppen ein erhebliches Wasserbindungsvermögen besitzt. Marquet (1956) vermutete *nach seinen klinischen Untersuchungen* zur Hörstörung bei Hypothyreosen einen Hydrops der Cochlea der durch die experimentellen Ergebnisse indirekt bestätigt werden konnte *Es handelt sich* jedoch mit Sicherheit nicht um einen endolymphatischen Hydrops wie man ihn als Ursache für den Morbus Menière ansieht – dafür bestehen bei der *hypothyreotisch* bedingten Schwerhörigkeit keinerlei Hinweise – aber mit hoher Wahrscheinlichkeit um einen Hydrops verschiedener Innenohrhohlräume dem konsequenterweise Elektrolytverschiebungen folgen können

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honären Fasern zu suchen sein. Von de Vos (1963) wurde nach dessen Ergebnissen bei der Hypothyreose eine Degeneration von Ganglienzellen nachgewiesen, worin der Autor die Ursache von Innenohrstörungen vermutet. Vergleicht man damit die histochemischen Ergebnisse zum *Enzymnachweis* z. B. der N-Azetyl-Glukosaminidase in den *Ganglienzellen* des Ganglion scarpae, so kann eine grob morphologische Schädigung der Zellen nicht in Betracht gezogen werden. Vielmehr scheint eine *Stoffwechseldrosselung*, die sich im Absinken der Fermentaktivität dokumentiert, im Vordergrund zu stehen. Nach autoradiographischen Untersuchungen haben die Ganglienzellen des *Ganglion spirale* den höchsten Eiweissumsatz von allen Innenohrstrukturen (Plester 1960; Meyer zum Gottesberge und Plester 1961; Koburg und Plester 1962*a*, *b*; Plester, Koburg und Hempel 1962; Maurer und Koburg, 1964), und zwar nimmt die Umsatzrate von Aminosäuren in den Ganglienzellen von der Basalwindung zur Apikalwindung ab, was möglicherweise mit der grösseren funktionellen Belastung der Basalwindung zusammenhängt (Koburg und Meyer zum Gottesberge 1964). *Die Inkorporation* von H_3-Aminosäuren in die Ganglienzellen nimmt zur Spitze hin etwa um 30% ab, während die Resorptionsfähigkeit der Stria vascularis für *K eine Steigerung von der Basal- zur Apikalwindung zeigt (Meyer zum Gottesberge, Rauch und Koburg, 1965).

Man kann sich somit vorstellen, dass die durch die Hypothyreose ausgelöste Herabsetzung der Proteinsynthese, wie bereits angedeutet, einen entscheidenden Einfluss auf die Funktionsfähigkeit der Ganglienzellen besitzt.

Zudem fällt ein zweiter Befund im Bereich des Nerven auf, dem mutmasslich eine eher mechanisch erklärbare Bedeutung zukommt. In unmittelbarer Nähe des Nerven, in der Umgebung des Plexus cochlearis, lassen sich häufig teilweise perjodatreaktive und/oder hyaluronidasesensitive Substanzen beobachten, deren Auswirkung auf den Nerven hinsichtlich einer Funktionsbeeinträchtigung zwei *Interpretationsmöglichkeiten* zulassen. Es wäre denkbar, dass durch das hohe Wasserbindungsvermögen der Hyaluronsäure ein hydropischer Zustand in der Umgebung des Nerven ausgelöst wird, der zu Diffusionsstörungen der Schwannschen Zellen und damit zu einer Beeinträchtigung der Leitfähigkeit des Nerven führt. Darüberhinaus bestände die Möglichkeit, dass Nervanteile im knöchernen *Modiolus und besonders in den Rosenthalschen* Kanälchen der Lamina spiralis ossea durch die Hydropie des umgebenden Gewebes komprimiert werden. So würde eine Störung der Reizleitung als Sekundärfolge der Hydropie im Bereich des Möglichen liegen. Ein Phänomen, welches auch als Ursache für die sog. Bell'sche Facialislähmung diskutiert wird.

Zuletzt erhebt sich die Frage, auf welchem Wege die sauren Mukosubstanzen sowie Muko- und Glukoproteide in die Skalen des Innenohres gelangen und auf welche Weise diese die Peri- und Endolymphräume wieder verlassen. Bevor verschiedene Möglichkeiten des Stofftransportes diskutiert werden sollen, muss festgestellt werden, dass auch heute noch keine vollständige Klärung dieses Problems herbeigeführt werden konnte. Insgesamt gesehen besitzt der Ductus cochlearis mit seinen spezialisierten Wandabschnitten sezernierende und resorbierende Funktionen. Als hypothetischer Bildungsort für die Endolymphe werden die Stria vascularis, Sulcus spiralis externus, Prominentia spiralis, Liquor cerebrospinalis, Reissner Membran (aus der Perilymphe) angenommen, wofür mancherlei Gründe sprechen, die hier nicht näher erörtert werden können (Lit. s. Rauch, 1964). Die Resorption der Endolymphe scheint überwiegend im Saccus endolymphaticus zu erfolgen, ist aber wohl auch in der Stria vascularis möglich, die einen *entsprechenden morphologischen* Aufbau mit erheblicher Vergrösserung der Oberfläche *zur Endolymphe hin auf*weist. Die Entstehung der Perilymphe lässt nach *Werner (1940)* drei Möglichkeiten zu: 1. *aus dem Liquor* cerebrospinalis, 2. aus Ge-

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möglichkeit für eine verzögerte Rückresorption der MPS aus der Perilymphe.

Die in der *Endolymphe histochemisch* bestimmten MPS werden mutmasslich zu einem grossen Teil im Saccus endolymphaticus resorbiert zumal sich aus den experimentellen Ergebnissen eine Anhäufung saurer Mukosubstanzen in der Sacculichtung bestimmen lässt. Eigene autoradiographische Untersuchungen am Saccus endolymphaticus erbrachten eine hohe Inkorporationsrate für H_3-markierte Aminosäuren die sich besonders in den Epithelien der Pars intermedia sowie im subepithelialen Raum und in einigen der sog. freien Zellen dokumentierte. In Anlehnung an die grundlegenden Arbeiten von Guild (1927 *a, b*) sowie Publikationen von Mygind (1948) Altmann und Waltner (1950) Saxén (1951) Arnvig (1951), Lundquist et al. (1964*a, b*) Lundquist (1965) wurden zwei „phagozytierende Systeme" im S. e. angenommen die Pars intermedia und die sog. freien Zellen (Haubrich und Koburg, 1966 Koburg et al. 1967) *Erwartungsgemäss besitzen Zellen* die für einen aktiven Stofftransport, wie sie die Resorption darstellt, einen hohen Eiweissumsatz, der in diesen Experimenten bestätigt wurde. Rudert (1969*a, b*) brachte radioaktiv markiertes Meerschweinchenelweiss sowie H_3-Aminosäuren (Lysin Glycin) in den Ductus *cochlearis* ein und beobachtete anschliessend die Resorption in den Epithelien der Pars intermedia und in den Zellen des darunterliegenden Bindegewebes. In Übereinstimmung zu den autoradiographischen Befunden wiesen Schätzle und Haubrich (1966) eine hohe Fermentaktivität in der Pars intermedia der S. e. und in den sog. freien Zellen nach. Eine besonders starke Aktivität zeigte die *N-Azetyl-Glukosaminidase und* unspezifische Esterase. Beide Fermente nahmen unter *Mangel* an Schilddrüsenhormonen ab. Vielleicht ein weiteres Indiz für den verzögerten Abbau und die behinderte Rückresorption der Mukopolysaccharide in den beschriebenen Strukturabschnitten des Saccus endolymphaticus.

Die am hypothyreoten Meerschweinchen erzielten Untersuchungsergebnisse eröffnen sektorförmig einen Einblick in die morphologisch nachweisbaren Strukturalterationen des Innenohres, die einige neue Erkenntnisse zur Entstehung der Schallperzeptionsstörung unter *Schilddrüsenhormonmangel vermitteln* andererseits aber auch weitere *Fragen auf*kommen lassen die durch elektrophysiologische und biochemische Arbeitsmethoden vielleicht beantwortet werden können. Am Schluss soll eine *Zusammenfassung der Be*funde und ihrer Interpretationsmöglichkeiten dargestellt werden.

a) Das im Vordergrund stehende pathomorphologische-histochemische Substrat ist die *Ablagerung von hyaluronidasesensitiven* metachromotropen Mukosubstanzen in den verschiedenen Skalen des Innenohres und im Bereich des Plexus cochlearis in unmittelbarer Nachbarschaft des N. acusticus. Durch die Anhäufung von sauren MPS kann sich infolge des hohen Wasserbindungsvermögens dieser *Substanzen ein allgemeiner Hydrops des In*nenohres entwickeln. *Zum anderen werden durch die* anionische *Polyelektrolytwirkung* der sauren MPS Verschiebungen von Kalium- und Natriumionen zwischen Peri- und Endolymphe möglich, deren normale Relation eine wichtige Voraussetzung für den normalen *Hörvorgang darstellt*.

Durch die Anhäufung saurer Mukosubstanzen mit grösseren Koacervaten in unmittelbarer Nähe des N. acusticus *kann* dieser *komprimiert werden* besonders in den sehr dünnen Rosenthalschen *Kanälchen* was zu einer Behinderung des notwendigen „axonal flow" aus der *Ganglienzelle* in das zugehörige Axon führt und damit einer Funktionsbeeinträchtigung Vorschub leistet. Zudem wird sich die Hydropie des umgebenden Gewebes im Bereiche des Nerven in einer *Diffusionsstörung* für den *Stoffwechselaustausch der Schwann*schen Zellen negativ bemerkbar machen.

Letztlich *erhält* die Anhäufung saurer Mukosubstanzen *im* Bereiche des Tractus arteriosus et venosus (Plexus cochlearis) Beweis-

fässen der Perilymphräume 3 aus der Endolymphe. Die meisten Untersuchungen sprechen für eine Produktion der Perilymphe aus den zahlreichen die Perilymphräume umgebenden Gefässe Eine ausführliche literaturhistorische Darstellung der verschiedenen Hypothesen über Sekretion und Resorption von Innenohrflüssigkeiten hat Rauch (1964) gegeben

Die in unmittelbarer Nähe des Plexus cochlearis (Balogh und Koburg, 1965) mit seinem Tractus spiralis arteriosus und venosus gelegenen hyaluronidasesensitiven Mukosubstanzen lassen sich aufgrund der autoradiographischen und fermenthistochemischen Untersuchungen (s auch Schätzle und v Westernhagen 1968) in Entstehung und Weitertransport gut erklären Nach Meinung von Balogh und Koburg findet sich im Plexus cochlearis ein sehr hoher Eiweissumsatz der bei manchen Tieren mit der Höhe der Umsatzraten in Ganglienzellen des Ganglion spirale vergleichbar ist Zudem entspricht der hohen Inkorporationsrate an H_3-Aminosäuren eine reiche Fermentausstattung mit DPNH und TPNH sowie LDH Morphologische und stoffwechseldynamische Vergleiche verschiedener Strukturen deren leptomeningeale Herkunft gesichert erscheint (z B Aderhaut des Auges Plexus chorioideus) mit dem Plexus cochlearis lassen weitgehende Übereinstimmung erkennen Balogh und Koburg nahmen daher eine sekretorische Funktion dieses stark ausgebildeten Gefässplexus an wofür eindrucksvoll die festgestellten Ansammlungen von Mukopolysacchariden in der unmittelbaren Umgebung des Plexus sprechen

Der Weitertransport der MPS vom Plexus cochlearis dürfte entlang der Nerven über das Ganglion spirale bis zu den Sinneszellen möglich sein ein Weg den Jampolski (1935) Kley (1951) und Svane Knudsen (1958) für möglich hielten Die sauren MPS können somit vermehrt in den Tunnelraum hineingelangen dessen früher als Cortilymphe bezeichneter Inhalt nach elektronenmikroskopischen Untersuchungen von Ilberg (1968*b*) identisch mit der Perilymphe ist d h es handelt sich um eine natriumreiche und kaliumarme Flüssigkeit Man kann also davon ausgehen dass eine freie Kommunikation des sog Cortilymphraumes mit der Scala tympani über die Habenula perforata entlang der Nervenfasern bis zu den inneren Haarzellen existiert Ein zweiter Transportweg ergibt sich aus den Untersuchungen von Ilberg über die Scala tympani die ja in Verbindung mit der Scala vestibuli steht so dass auch aus diesem Perilymphraum saure Mukosubstanzen in den Cortilymphraum gelangen können.

Die Produktion der MPS in die perilymphatischen Räume dürfte über das reich entfaltete Gefässystem der perilymphatischen Skalen vor sich gehen umsomehr als bei der Hypothyreose eine Erhöhung der Mukopolysaccharide im Blutserum bekannt ist

Nach experimentellen Untersuchungen von Ilberg (1968*a*) ist bewiesen dass über das Ligamentum spirale mit seinen breiten Interzellularräumen beide Skalen miteinander kommunizieren das Bindegewebe des Lig. spirale quasi einen grossen Schwamm darstellt der von Perilymphe durchdrungen wird eine Vorstellung, die von Tonndorf et al (1962) Spoendlin und Balogh (1964) Cimino und Grisanti (1967) Ilberg (1968*a*) Vosteen (1970) entwickelt wurde Aus dieser Verbindung beider Skalen wird die Verteilung der Mukosubstanzen in allen perilymphatischen Räumen verständlich

Die Resorption der Makromoleküle wie sie die Mukopolysaccharide darstellen könnte nach fermentativer Aufspaltung der Mukosubstanzen erfolgen Voraussetzung ist eine ungestörte für die MPS substratspezifische Fermentaktivität die bei den experimentellen Untersuchungen am Beispiel der β-Galaktosidase der β-Glukuronidase und N Azetyl Glukosaminidase dargestellt wurde Während die ersten beiden Glykosidasen in ihrer Aktivität im Gewebe gegenüber den Kontrolltieren weitgehend unverändert sind nimmt die Glukosaminidase sehr deutlich ab Vielleicht wäre diese Tatsache u a eine Erklärungs

11 Zusammenfassung

Seit langer Zeit ist Schwerhörigkeit als fakultatives oder obligates Symptom bei Schilddrüsenerkrankungen bekannt ohne dass bislang eindeutige morphologische Befunde zur Deutung der Hörminderung erhoben worden sind. Zu experimentellen morphologischen Studien werden 70 thyreoidektomierte Meerschweinchen verwendet, die als Modell für die primäre Hypothyreose infolge quantitativer Störung der Hormonbildung beim Menschen gelten können Nach Tötung der Tiere in verschiedenen Zeitabständen werden mit histochemischen Methoden verschiedene Glykosidasen (β-Galaktosidase β-Glukuronidase N Azetyl-β-Glukosaminidase) sowie unspezifische Esterasen und Aryl-Sulfatasen Sulfhydryl-Gruppen und Mukosubstanzen in der Cochlea und im Saccus endolymphaticus bestimmt. Folgende Ergebnisse lassen sich erheben: Durch Ablagerung von hyaluronidase sensitiven metachromotropen Mukosubstanzen in den Skalen des Innenohres wird mutmasslich das Verhältnis Kaliumionen zu Natriumionen in Endolymphe und Perilymphe infolge der anionischen Polyelektrolytwirkung der sauren Mukopolysaccharide gestört Darüberhinaus kommt es zu einem Hydrops der erschiedenen Innenohrhohlräume durch die stark hydropen Eigenschaften der sauren MPS mit konsekutiver Verschiebung der Elektrolytverhältnisse (Elektrochemische Theorie) Die in der Umgebung des N acusticus angehäuften sauren MPS können infolge der Hydropie zu Kompressionserscheinungen des Nerven besonders in den Rosenthalschen Kanälchen der Lamina spiralis ossea führen (mechanische Theorie) Einzelne Enzyme (unspezifische Esterase N Azetyl-β-Glukosaminidase) werden in ihrer Aktivität in verschiedenen Abschnitten der Cochlea und des Saccus endolymphaticus durch den Hormonmangel beeinträchtigt was auf die fermentinduktive Eigenschaft der Schilddrüsenhormone bezogen werden kann

Die Vermehrung der sauren MPS in den verschiedenen Skalen der Cochlea und des Saccus endolymphaticus lässt sich aus einer vermehrten Produktion und einer verminderten Resorption der Stoffe erklären wofür auch die Ansammlung metachromotropen Materials im S e spricht. Nach den morphologischen Ergebnissen lässt sich zumindest ein Sekretionsort der sauren MPS im Bereich des Plexus cochlearis lokalisieren Alle angegebenen Befunde können eine Erklärung für die häufiger anzutreffende Innenohrschwerhörigkeit geben. Die seltenere Schalleitungsstörung dürfte auf eine myxomatöse Veränderung der Mittelohrschleimhaut mit konsekutiver Versteifung der Gehörknöchelchen zu beziehen sein Letztlich wird aus den Befunden die teilweise Reversibilität der Schwerhörigkeit nach Hormonsubstitution verständlich.

kraft für das sekretorische Leistungsvermögen dieser Innenohrstruktur

b) Ein weiteres Merkmal hypothyreotisch *bedingter Störung* des Innenohrstoffwechsels ist der erhobene Enzymstatus der unspezifischen Esterasen Aryl Sulfatasen und Glykosidasen Insgesamt sind die Befunde diskreter als beim Stoffwechselmetabolismus der Mukosubstanzen So werden mehr die Aktivitäten der unspezifischen Esterase und die N *Azetyl-Glu*kosaminidase reduziert als die der Glukuronidase und Galaktosidase Die Aktivitätsbeeinträchtigung der Fermente dürfte im Zusammenhang der enzyminduktiven Wirkung der Schilddrüsenhormone und der herabgesetzten Proteinsynthese bei der Hypothyreose zu sehen sein Mit entscheidend scheint die stark verminderte Aktivität der Glukosaminidasen zu sein die für einen Hauptbestandteil der sauren MPS des N Azetyl-Glukosamin substratspezifisch ist

Wenn auch die Bedeutung der dargestellten Fermente für die Funktionen des Innenohres noch weitgehend ungeklärt ist wird jedoch eine Störung des Fermenthaushaltes nicht ohne Folgen für die Funktion bleiben können

c) Die Produktion und Resorption der Mukopolysaccharide in den Innenohrräumen lassen sich aufgrund der heutigen Ansichten über aktive und passive Leistung der für den Stofftransport spezialisierten Wandbestandteile des Ductus cochlearis und der beiden perilymphatischen Skalen deuten Ein sicherer Weg der Produktion dürfte am Plexus cochlearis über die Nervenfasern in den sog Cortilymphraum und damit zu der Basis der Haarzellen verlaufen Andere Wege liegen mit grosser Wahrscheinlichkeit ebenfalls vor wie sich aus den Erörterungen zur Sekretion und Resorption der Innenohrflüssigkeiten entnehmen lässt Die Resorption der Mukopolysaccharide aus der Scala media geht wahrscheinlich zu einem Grossteil über den Saccus endolymphaticus in dem alcianblaues, hyaluronidasesensitives Material festgestellt worden ist Es ist durchaus denkbar dass die Resorption infolge einer verzögerten Aufschlusselung der MPS durch die herabgesetzte Fermentaktivität in ihrem Geschwindigkeitsablauf beeinflusst wird

d) Durch die myxomatöse Verdickung der Mittelohrschleimhaut die nach experimentellen und klinischen Ergebnissen relativ selten vorkommt lässt sich zwanglos infolge von Versteifung der Gehörknöchelchen eine resultierende Schalleitungsstörung erklären

Alle Veränderungen haben nur Gültigkeit in der Übertragung auf den Menschen bei der im Kindes oder Erwachsenenalter erworbenen Hypothyreose infolge qualitativ gestörter Hormonbildung Sie besitzen keine Aussagekraft für die Genese der endemischen Hörstörung oder des sog Pendred Syndrom Sie berücksichtigen auch nicht die durchaus möglichen hypothyreotisch bedingten zentralen Störungen Die Untersuchungen sind jedoch erste Schritte in der Aufklärung hormoneller Einflüsse auf das Innenohr soweit sie mit morphologischen Methoden fassbar sind Sie können eine Erklärung für die oft zu beobachtende Reversibilität der Innenohrstörungen nach Hormonsubstitution geben

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12 Summary

It has been known for a long time that hearing deficits may coexist in patients with thyroid disease but without definite morphologic evidence present to correlate gland dysfunction with hearing disturbances To clarify this relationship between thyroid dysfunction and hearing disturbances the guinea pig was employed as an experimental model 70 animals were thyroidectomized and maintained in a hypothyroid state for varying periods of time The animals were then sacrificed and various histochemical studies then performed These studies included analysis for glycosidase (β-galactosidase β-glucuronidase *n* acetyl β-glucosamide) non specific esterases sulfatases sulfhydryl groups as well as mucous substances within the cochlea and saccus endolymphaticus of the experimental animals Results indicated that hyaluronidase sensitive mucous substances were increased in the scala of the inner ear As a consequence of increased deposition of acid mucopolysaccharides the relationship of potassium to sodium in endolymph and perilymph was found markedly altered Marked swelling of the chambers of the inner ear was noted and believed to represent hydropic induction by acid mucopolysaccharide—with consequent alteration of electrolyte relationships (Electrochemical Theory)

Acid mucopolysaccharide was also found in significant quantities in the region of the acoustic nerve producing a compression phenomenon of the nerve This was most marked in the region of Rosenthal s canal of the lamina spiralis ossea. This *finding supports* a Mechanical Theory for hearing disturbance Lowered levels of enzymes (non specific esterases *n* acetyl β-glucosamidase) were found in the cochlea and saccus endolymphaticus and were attributed to lack of thyroid hormone initiating enzyme activity

The increase in acid mucopolysaccharide in the different scala of the cochlea and saccus endolymphaticus was explainable by both increased production and altered resorption These factors were also in evidence by the collections of metachromatic granules in the saccus endolymphaticus A secretory site for acid mucopolysaccharide was uncovered in the region of the plexus cochleans.

Findings during the present investigation provided morphologic evidence for inner ear disease in association with thyroid dysfunction Also noted during the present study was myxomatous change in the middle ear mucosa with consequent stiffening of the ossicles Thus both neurosensory and conductive hearing losses could be explained by the present findings

Replacement hormone therapy was given to a group of the experimental animals and was found to modify the previously noted changes in the inner and middle ears

The present study has indicated that thyroid dysfunction can result in hearing disturbances in experimental models Further work will be performed to further define this relationship in both experimental and clinical levels of endeavor

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SUPPLEMENT 333

Experimental Studies on the Nerve—Sensory Cell Relationship during Degeneration and Regeneration in Ampullar Nerves of the Frog Labyrinth

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BY

LARS GLEISNER, M. D. and
JAN WERSÄLL, M. D.

From The Department of Otolaryngology and The King Gustav V Research Institute, Karolinska sjukhuset, Stockholm, Sweden

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Introduction

The dependence of receptor organs on their nervous connections has been extensively studied throughout the century since Ranvier (1875) found that taste buds disintegrate after the section of gustatory nerves. A review of the results of experimental work on different types of receptors after peripheral nerve degeneration and regeneration was presented by Zelená (1964). The receptor organs investigated were of both the primary (cutaneous and muscle receptors) and the secondary type (taste buds and lateral-line organs). In all these sensory cells signs of degeneration were found after denervation, and in many cases regeneration was induced by reinnervation. The evidence was consistent with the hypothesis that nerve endings exert a trophic effect on the maintenance and eventually on the differentiation of receptor organs.

In the case of the lateral-line system, degeneration of sensory cells at various periods after transection of the nerves, followed by reinnervation and regeneration, has been reported by several authors, though others have asserted that denervation does not necessarily result in complete loss of sensory organs. Earlier studies on lateral line organs in amphibia were reviewed by Wright (1951), who concluded that this sensory system can persist for months after repeated nerve section. The effect of denervation in long-term experiments was considered to consist of a decrease in the size of the denervated organs by a regressive process involving atrophy, dedifferentiation and eventually total degeneration of the whole organ. This suggests that the nerve exerts a definite trophic action on these sensory organs but that the effect of its removal is not immediate but long-term. This is consistent with the results of Speidel's research on frog tadpoles (1964).

As far as the vestibulo-cochlear system is concerned, there is little information available about the fate of vestibular sensory cells after lesions of the nerves. A recent study in squirrel monkey (Igarashi & Miata, 1972) indicates that degeneration of the crista sensory epithelium occurs after sectioning of more than 75% of the ampullar nerve. Gribenski (1963) reported advanced crista degeneration one month after destruction of the ganglion of Scarpa in frog. The organ of Corti in cat remains intact for several months after sectioning of the cochlear nerve (Spoendlin & Gacek, 1963): this finding is discussed later in the light of recent findings by Spoendlin (1971).

In a number of studies of the effects of nerve division in the vestibulo-cochlear system interest has been centred chiefly on the relations between afferent and efferent fibres as disclosed by light and electron microscopy (Rasmussen & Gacek, 1958; Schuknecht et al., 1959; Gacek, 1960; Kimura & Wersäll, 196..; Smith & Rasmussen, 1963, 1965, 1968; Spoendlin, 1966, 1971). Robbins et al., (1967) demonstrated the existence of efferent nerve fibres to the labyrinthine sensory areas in the bullfrog in a study of the degeneration of fibres in the transected vestibular nerve. Hillman (1969) found efferent nerve fibres connecting the cerebellum and brainstem nuclei with the sensory cells of the macula sacculi in the frog. The effect of cutting the vestibular nerve on the sensory cells was not described in this report. A tendency for complete morphological and functional restoration after dividing the vestibular nerve in frogs was observed earlier by Sperry (1945).

After transposing nerves from one ampulla of the labyrinth to another in the frog, Gribenski (1963) found a regeneration from one nerve to a different end organ, and followed the physiological effect of this transformation of ampullar nerve fibres. Even today little is known about the

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The present study was undertaken to examine (1) the effect of division of peripheral ampullar nerves on the fine structure of synapses and sensory cells (2) the capacity of the nerve fibres to regenerate under various experimental conditions and (3) the structural changes that occur in the sensory cells after denervation and during reinnervation.

Material and Methods

The study was performed on the adult frog (*Rana temporaria*). The normal anatomy of the labyrinth of this species is similar to that of the bullfrog as described by Gesler et al. (1964). Thus the anterior branch of the vestibular nerve gives off separate branchlets to the anterior vertical and horizontal cristae, and the maculae of the utricle and saccule. This part of the labyrinth is readily accessible for experimental work.

Two sets of experiments were performed. In one set one or both ampullar nerves were sectioned and the nerves, synapses and sensory cells were examined at intervals during the degenerative phase and during regeneration of the nerve fibres. In the second set of experiments the two ampullar nerves were divided and the proximal stump of the horizontal nerve was brought into contact with the distal end of the anterior vertical nerve. In one case the anterior nerve was actually attached to the horizontal distal stump. The operations are shown schematically in Fig. 1. Twenty animals survived the surgical procedure without apparent complications and could be followed until the labyrinths were fixed *in vivo* and submitted to histological examination. In a few other specimens there were post-operatively signs of loss of function of most or all parts of the labyrinths subjected to limited surgery; some of these animals died after a few days. In such cases inflammatory cells invading the endolymphatic spaces and the surrounding tissues were found on microscopical examination, and these animals were excluded. Other animals survived for long period and their physiological responses could be tested during the course of the postoperative period but, because of spontaneous death at later stages, they were also excluded from electron microscopical examination as post-mortem changes were likely to interfere with signs of intravital degeneration.

Operative Procedures

The ampullar nerves were exposed in the curarized frog (2–3 mg of *d*-tubo-curarine per kg body weight) which was kept moistened. The operation was carried out as described by McNally & Tait (1933) and Gribenski (1963): thus the mucosa of the palate was incised, part of the chondrous capsule of the labyrinth was removed and the bone capsule was drilled away over the anterior branch of the nerve in the region of the cristae. The endosteum and the membrane limiting the perilymphatic space were incised. The nerves to the anterior vertical and the horizontal

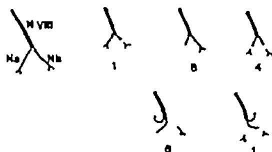


Fig. 1. Schematic drawing of the normal innervation pattern of the anterior part of the right labyrinth (*central view*), the numerals refer to the numbers of specimens in each type of operation.

Abbreviations used in the figures:

HC hair cell (sensory cell), SC supporting cell, N VIII anterior branch of the vestibular nerve, Na anterior vertical ampullar nerve, Nh horizontal ampullar nerve, N ampullar nerve, NF nerve fibre, NT nerve terminal, ANe afferent nerve ending, ENe efferent nerve ending, BM basement membrane, SB synaptic body, SV synaptic vesicles, DS dense substance, Mi mitochondria.

relation between the nerve endings and the sensory cells during degeneration and regeneration of nerve fibres in the vestibular system

In a series of studies, Sperry has examined the relation between certain central nuclei and peripheral end-organ on the one hand and on the other the ability of afferent nerve fibres to regenerate and restore the normal functional relationship between the end organ and the central nervous system. The results suggest that a chemoaffinity is the basic mechanism regulating the growth and organization of nerve fibres and their connections (Sperry 1963) Weiss (1955) considered it possible that there is some reorganization through an influence from the periphery upon more central portions of the nervous system during the regeneration phase Together with Pillai (1965) he also studied the ultrastructural changes in axons in which constrictions were made to prevent the proximo-distal displacement of axonal contents first described by Cajal (1928) and later by Weiss & Hiscoe (1948) It has later been shown by different methods that transport of several axonal components occurs in both directions and at different velocities (see e.g. Lubińska 1964 Grafstein 1969) Although the substances which exert the presumed neurotrophic effect on other nerves or end organs have not been identified, there is accumulating evidence for a nutritive and regulatory role of axonal transport mechanisms as a basis for such an hypothesis The incitement to the present study was provided by Gribenski s above mentioned studies on frogs (1963) in which the functional results of labyrinthine experiments are described The behavioural physiology of the vestibular apparatus in frog was elucidated long ago by Tait & McNally (1925) by means of simple rotatory sliding and tilting tests, and the roles played by the different sensory formations in the labyrinth were shown by selective ablation experiments (McNally & Tait, 1925 and 1933). The results were confirmed by Gribenski who in 1963 published a review of the earlier work, together with a summary of a series of experiments of his own on the function of the semicircular canals of the frog. Electrophysiological studies on these organs were made by Ledoux who recorded afferent mass potentials from the ampullar nerves and tried to correlate the results of clinical vestibular tests with the patterns of peripheral nerve activity following different stimuli (Ledoux, 1958)

Gribenski completed his studies with a series of animals in which nerves from one ampulla were transposed to another resulting in misdirected reflexes after the inappropriate reinnervation This experiment is briefly described here together with some of the basic physiological responses to stimulation

In a normal frog rotatory acceleration in the horizontal plane leads to a perstimulatory deviation of the head and an incurvation of the body in the sense opposed to the rotation the post stimulatory reaction is reversed On tilting forwards through a transversal axis, the animal reacts by extending its arms and raising its head this position is maintained when the tilting is stopped. After elimination of the function of the left horizontal ampulla, the animal does not turn its head to the left on horizontal rotatory accelerations the deviations to the right are quite normal After elimination of the function of the left anterior vertical ampulla, the frog reacts on tilting forwards by dipping its head downwards to the left with a torsion of the spine owing to inadequate extension of the left arm and to increased extension of the right leg, when the tilting is stopped a normal pose for that inclination is assumed When Gribenski let the left horizontal nerve innervate the anterior vertical ampulla (after operation R" derived from the word régénération) a new reaction (reaction R ") was found on tilting about 2 weeks after the operation The head then deviated to the right side and by repeated accelerations causing endolymph movement in the vertical canals, the animal incurved and sometimes began to walk to that side All these reactions are interpreted as being due to an increase in impulse activity in the left horizontal nerve activated from the reinnervated anterior vertical crista This reaction reaches a maximum at about 3–4 weeks after the operation

The present study was undertaken to examine (1) the effect of division of peripheral ampullar nerves on the fine structure of synapses and sensory cells (2) the capacity of the nerve fibres to regenerate under various experimental conditions and (3) the structural changes that occur in the sensory cells after denervation and during reinnervation.

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The study was performed on the adult frog (*Rana temporaria*). The normal anatomy of the labyrinth of this species is similar to that of the bullfrog as described by Geisler et al. (1964). Thus the anterior branch of the vestibular nerve gives off separate branchlets to the anterior vertical and horizontal cristae, and the maculae of the utricle and saccule. This part of the labyrinth is readily accessible for experimental work.

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Operative Procedures

The ampullar nerves were exposed in the curarized frog (2–3 mg of d-tubo-curarine per kg body weight) which was kept moistened. The operation was carried out as described by McNally & Tait (1933) and Gribenski (1963), thus the mucosa of the palate was incised, part of the chondrous capsule of the labyrinth was removed and the bone capsule was drilled away over the anterior branch of the nerve in the region of the cristae. The endosteum and the membrane limiting the perilymphatic space were incised. The nerves to the anterior vertical and the horizontal

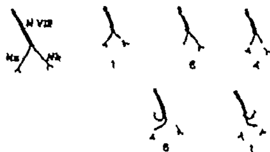


Fig. 1. Schematic drawing of the normal innervation pattern of the anterior part of the right labyrinth (*ventral view*); the numerals refer to the numbers of specimens in each type of operation.

Abbreviations used in the figures.

HC hair cell (sensory cell). SC supporting cell. N VIII anterior branch of the vestibular nerve. Na – anterior vertical ampullar nerve. Nh horizontal ampullar nerve. N ampullar nerve. NF nerve fibre. NT – nerve terminal. ANe afferent nerve ending. ENe – efferent nerve ending. BM basement membrane. SB – synaptic body. SV synaptic vesicles. DS dense substance. Mi mitochondria.

relation between the nerve endings and the sensory cells during degeneration and regeneration of nerve fibres in the vestibular system

In a series of studies, Sperry has examined the relation between certain central nuclei and peripheral end-organ on the one hand and on the other the ability of afferent nerve fibres to regenerate and restore the normal functional relationship between the end organ and the central nervous system The results suggest that a chemoaffinity is the basic mechanism regulating the growth and organization of nerve fibres and their connections (Sperry 1963). Weiss (1955) considered it possible that there is some reorganization through an influence from the periphery upon more central portions of the nervous system during the regeneration phase Together with Pillai (1965) he also studied the ultrastructural changes in axons in which constrictions were made to prevent the proximo-distal displacement of axonal contents first described by Cajal (1928) and later by Weiss & Hiscoe (1948). It has later been shown by different methods that transport of several axonal components occurs in both directions and at different velocities (see e.g. Lubińska, 1964 Grafstein 1969). Although the substances which exert the presumed neurotrophic effect on other nerves or end organs have not been identified there is accumulating evidence for a nutritive and regulatory role of axonal transport mechanisms as a basis for such an hypothesis. The incitement to the present study was provided by Gribenski's above-mentioned studies on frogs (1963) in which the functional results of labyrinthine experiments are described

The behavioural physiology of the vestibular apparatus in frog was elucidated long ago by Tait & McNally (1925) by means of simple rotatory sliding and tilting tests, and the roles played by the different sensory formations in the labyrinth were shown by selective ablation experiments (McNally & Tait, 1925 and 1933). The results were confirmed by Gribenski who in 1963 published a review of the earlier work, together with a summary of a series of experiments of his own on the function of the semicircular canals of the frog. Electrophysiological studies on these organs were made by Ledoux who recorded afferent mass potentials from the ampullar nerves and tried to correlate the results of clinical vestibular tests with the patterns of peripheral nerve activity following different stimuli (Ledoux, 1958)

Gribenski completed his studies with a series of animals in which nerves from one ampulla were transposed to another resulting in misdirected reflexes after the inappropriate reinnervation This experiment is briefly described here together with some of the basic physiological responses to stimulation

In a normal frog rotatory acceleration in the horizontal plane leads to a perstimulatory deviation of the head and an incurvation of the body in the sense opposed to the rotation the poststimulatory reaction is reversed On tilting forwards through a transversal axis, the animal reacts by extending its arms and raising its head this position is maintained when the tilting is stopped. After elimination of the function of the left horizontal ampulla, the animal does not turn its head to the left on horizontal rotatory accelerations the deviations to the right are quite normal. After elimination of the function of the left anterior vertical ampulla the frog reacts on tilting forwards by dipping its head downwards to the left with a torsion of the spine owing to inadequate extension of the left arm and to increased extension of the right leg when the tilting is stopped a normal pose for that inclination is assumed When Gribenski let the left horizontal nerve innervate the anterior vertical ampulla (after operation "R" derived from the word régénération) a new reaction (reaction "R") was found on tilting about 2 weeks after the operation. The head then deviated to the right side and, by repeated accelerations causing endolymph movement in the vertical canals, the animal incurved and sometimes began to walk to that side All these reactions are interpreted as being due to an increase in impulse activity in the left horizontal nerve activated from the reinnervated anterior vertical crista. This reaction reaches a maximum at about 3–4 weeks after the operation

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N VIII Na Nh 1 8 4 6 1

Fig. 1 Schematic drawing of the normal innervation pattern of the anterior part of the right labyrinth [illegible]; the numerals refer to the numbers of specimens in each type of operation.

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cristae were isolated from the accompanying vessels and one or both nerves were divided, depending on the type of experiment. In one set of experiments the proximal stump was left in contact with the distal stump while in the other one of the proximal stumps was transposed to the distal stump of the other ampullar nerve. In order to increase the distance between the two stumps in the transposition experiments, the distal stump that should not reinnervate the crista was displaced and deflected proximally The mucosal flap was applied and sutured over the operation cavity

The frogs were then kept at room temperature (about 20 C) for varying periods. The animals surviving the procedure generally regained motility in a few hours. During the survival period they were kept moistened in small boxes, and fed with meal worms

The function of the vestibular system was examined by rotatory and tilting tests at various, repeated intervals after the operation the methods used were principally those of McNally & Tait (1925 1933) and Gribenski (1963) In the rotatory tests optokinetic stimuli were eliminated by placing the animals in a cylindrical non transparent box placed on a turn table In tests of the function of the anterior vertical cristae repeated tipping movements were made, causing utriculo-fugal endolymphatic streaming. These physical stimuli and the animal's responses were rated in a roughly standardized way without attempt to strict quantitative measurements. At intervals of between 6 hours and 46 days after the operation the animal was again curarized, the labyrinth was opened, the anatomy of the operation wound was examined, and the labyrinth was fixed *in situ* with ice-cold 1 per cent osmium tetroxide in Ringer's solution adjusted to the osmolarity of frog plasma. The endolymphatic space was opened and some fixative was introduced Immediately afterwards, the labyrinth was dissected and placed in the same osmium tetroxide solution and fixed for periods ranging from 30 minutes to 2 hours. The specimens were rinsed in Ringer's solution, dehydrated in ascending concentrations of alcohol and embedded in Epon as described by Luft (1956).

Thick sections were cut for survey purposes and stained with toluidine blue. Thin sections, cut with a LKB Ultrotome, were picked up on formvar-covered copper grids, stained with uranyl acetate and lead citrate (Reynolds, 1963) and examined in an Elmiskop I Photographs were taken in the electron microscope at magnifications of from ×600 to ×40 000 and further magnified during the copying procedure. Gevaert Scientia plates and Gevaert paper were used.

Results

Physiological Observations

All the frogs in which one or more ampullar nerve branches had been divided and on which functional tests were performed showed signs of loss of function of the corresponding crista similar to those originally described by McNally & Tait (1925 1933) and also by Gribenski (1963) and others When only the nerve to the *horizontal* crista was cut, loss of function of the ipsilateral horizontal canal was first observed about 1–2 weeks later the function of that canal seemed to reappear and over the next two weeks there was a progressive return to normal In some of the animals in which one of the ampullar nerves had been transposed to the other crista there was the corresponding type of functional impairment of both cristae followed after 2 3 weeks by signs of paradoxical innervation of the crista (Gribenski's "reaction R) Where the anterior vertical crista was innervated by the horizontal nerve there was thus a reaction indi-



Fig. 2. Survey of normal crista ampullaris with sensory cells, supporting cells and distal parts of the ampullar nerve which loses its myelin sheath close to the basement membrane.

cative of stimulation of the horizontal nerve when the ertical canal was stimulated. These signs of a paradoxical effect lasted for from a few days up to 2–3 weeks, there was then a steady recovery of normal function which was complete after a month or so. In a few animals there was no paradoxical response but a period of recovery of normal function similar to that found on simple section of the horizontal nerve.

Gross morphology of Vestibular Nerve after Transection

After fixation, the specimens were examined under a dissection microscope and further dissected in the Epon blocks. For a few days after simple division of one ampullar nerve there was a defect between the central and peripheral stumps owing to retraction of the latter. Three

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Fig. 4. Efferent nerve ending in contact with two sensory cells. The ending contains a large accumulation of synaptic vesicles. Presynaptic dense substance and subsynaptic sacs (arrows) can clearly be seen.



Fig. 5. Afferent nerve ending containing a large number of mitochondria. The synaptic body is surrounded by vesicles and complex in the form of three "feet" in contact with the presynaptic membrane.

from the transposed reinnervating nerve. The relations between the two nerves and the cristae increasingly resembled those in the normal structure.

Fine Structural Changes in Sensory Cells and Nerve Endings during De- and Regeneration

Normal controls

The fine structure of the sensory epithelia in the controls was essentially identical with that of normal cristae. The structural organization of the hair cells and their synaptic areas has been described by Wersäll et al. (1967) and is illustrated here for comparison with the experimental material in Figs. 2–5.

Degenerative phase

The degenerative phase was taken to be the first 5 post-operative days during which there was no evident regeneration in the most distal part of the distal stump. No distinction was made between the nerves that were only divided



Fig. 3. Normal sensory cell with afferent and efferent nerve endings.

or four days later, however, the continuity between the peripheral and the central stumps was restored. The distal part of the nerve never completely lost its stainability with osmium. About 7–8 days after division, fine fibres staining light brown appeared in the distal stump. They gradually increased in number and darkened until it was difficult to distinguish them from the normal nerve.

In those cases in which one of the branches was transposed from one ampulla to the other, reinnervation of the recently attached distal stump appeared at about the same time as after the simple division of the nerve. Some fibres also found their way from the reinnervated distal stump to the crista it originally innervated. Fibres also came from the original central stump of the ampullar nerve and mixed with those growing



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30 minutes (one animal). Already 30 minutes after transsection definite changes were observed in the distal stump of the nerve close to the site of the division (Fig. 6). The axons were oedematous, there was extensive disorganization of neurofibrils, the mitochondria showed evidence of degeneration and there was widespread splitting of the lamellae in the myelin sheaths. There were only minor changes in the unmyelinated part of the nerve fibres extending to the basement membrane, but some dark bodies without membrane structures were seen, and some vacuoles appeared in the axon (Fig. 7). The neurofibrils were mostly intact.

In the afferent nerve endings some of the vesicles had disintegrated between others there was oedema and other vesicles were clumped together. Even some of the mitochondria were slightly swollen with disintegration of the mitochondrial membrane (Fig. 8). The synaptic contact had not changed appreciably. The synaptic body was in normal contact with the plasma membrane on the presynaptic side in the hair cell, and was surrounded by synaptic vesicles. There appeared to be a decrease in the number of vesicles and in the size of coated vesicles and tubules surrounding the synaptic area. No other changes were found in the sensory cells themselves.

6 hours (one animal). 6 hours after the nerves had been divided the endings displayed marked changes (Fig. 9) these included oedematous swelling of the nerve endings, degeneration of mitochondria with swelling and disintegration of mitochondrial membranes, swelling and lack of contrast in the synaptic vesicles and disappearance of the dense part of vesicles that were of the dense type. The synaptic contact was intact and the synaptic bodies still maintained contact with the plasma membrane and were surrounded by synaptic vesicles.

The distal stump of the nerve branch showed signs of extensive disintegration (Fig. 10). The splitting of the myelin sheath and the degeneration of the axons had continued. Large dark bodies in the Schwann cells suggested that disintegration of some of the myelin had occurred. A few nerve fibres displayed remarkably little evidence of change.

18–20 hours (2 animals). After 18–20 hours, the unmyelinated part of the nerve fibres and the nerve endings exhibited severe degeneration. The mitochondria had lost most of their cristae. Some of them were swollen, while others were clumped together to form either irregular dense bodies surrounded by large vesicles, or large vacuoles (Fig. 11). Small filaments were observed in the nerve endings, whereas the number of vesicles was considerably reduced. The nerve endings had sometimes lost contact with the synaptic membranes or there was detachment of the nerve endings from the sensory cell, with wide spaces between them and defects in the plasma membrane of the nerve ending. Usually however there was still attachment at the site of the synaptic body. Synaptic bodies remained in the sensory cell surrounded by a few synaptic vesicles (Fig. 12).

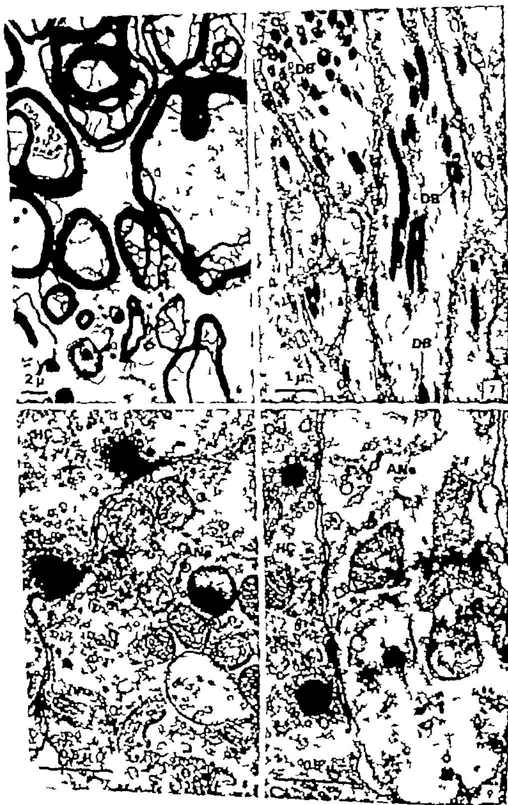
Efferent nerve fibres were found in the sensory epithelium and although oedema had appeared in the nerve endings, synaptic vesicles and mitochondria with only minor changes remained numerous (Fig. 13). The efferent nerve endings were still in contact with the sensory cells and the subsynaptic sacs on the sensory cell side of the synapse were intact. The supporting cells contained large accumulations of dark bodies—presumably débris from degenerating nerve endings and fibres. Even in the sensory cells there

Fig. 6. Cross-section of an ampullar nerve distal to the division. Note splitting of the myelin sheaths and disorganization of the axons (30 min post-op.).

Fig. 7. Longitudinal section of the distal nerve stump immediately under the basement membrane. Some dark bodies can be seen (30 min post-op.).

Fig. 8. Afferent nerve ending with swelling of mitochondria and slight oedema. Normal synaptic structure (30 min post-op.).

Fig. 9. Afferent nerve ending with marked oedematous swelling, degenerated mitochondria and some vesicles (6 h post-op.).



DB
DB
DB
2 μ
1 μ
7
HC
AN
AN
HC
9

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Fig. 15. Globular space (arrow) between sensory cells, here afferent nerve terminal is missing (24 h post-op.).
Fig. 16. Detail of Fig. 15: synaptic body with surrounding vesicles.
Fig. 17. Efferent nerve ending in contact with sensory cell. The synaptic apparatus normal (24 h post-op.).

Fig. 18. Degenerated fibres in distal stump of ampull[...] nerve. Note swollen Schwann cells with lactosomes (arrow[...] (3 d post-op.).
Fig. 19. Proximal to the lesion the same ampull[...] nerve as in figure 18 has a normal structure with no sig[...] of retrograde degen[...]

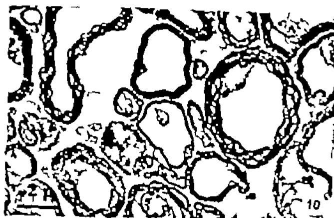








Fig. 10. Cross-section of distal nerve stump. The myelin lamellae are distorted, the axonal remnants condensed (6 h post-op.).

Fig. 11. Afferent nerve ending with irregular areas of condensation, formed by mitochondria and vacuoles (18 h post-op.).

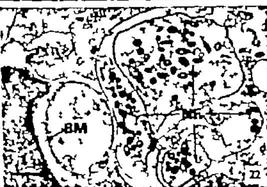
Fig. 12. Degenerating afferent nerve ending in synaptic contact with sensory cell (18 h post-op.).

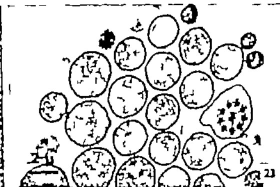
Fig. 13. Efferent nerve ending with minor signs of degeneration—slight oedema and some vacuoles (18 h post-op.).

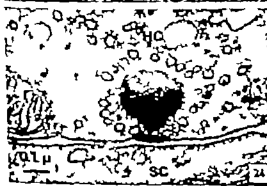
Fig. 14. Survey of sensory and supporting cells of essentially normal appearance. Some dark inclusions are seen in both types of cell (18 h post-op).

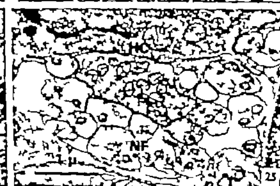

HC
1 μ
20

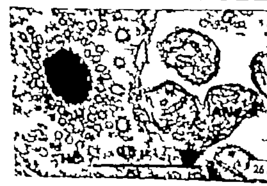

1 μ
21

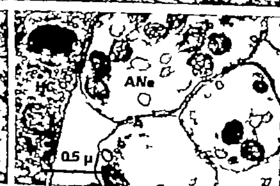

BM
22


23


HC
SC
24


HC
NF
25


26


HC
ANe
0.5 μ
27

appeared to be some increase in the number of dark bodies, but otherwise these cells were intact with normal sensory hairs, mitochondria and other structures (Fig. 14).

24 hours (? animals). After 24 hours, there were areas in which no afferent nerve endings could be found. Opposing sensory cells were separated by globular spaces (Fig. 15) some of these were located where the nerve endings had disappeared as indicated by synaptic bodies still surrounded by synaptic vesicles (Fig. 16) The efferent nerve endings appeared to be quite normal (Fig. 17) In one of the specimens there were no changes in the sensory and supporting cells other than those in the animals described above, while in the other several sensory cells were severely changed with marked swelling of the nuclei and the cytoplasm filled with vacuoles and multi vesicular bodies. Other sensory cells were apparently normal, although a few showed a shrinkage of the cytoplasm with high electron density which was still more intense in the nuclei. The supporting cells and the above-mentioned relationships between nerve endings and cells were the same as in the first specimen at the same stage The differences described might have been due to a change in the preparatory technique at a critical stage which is further discussed below

2 and 3 days (3 animals) In specimens taken 2 and 3 days after transsection there was evidence of progressive degeneration of afferent nerve fibres, terminal branches and nerve endings. Schwann cells in the distal stump of the nerve showed signs of phagocytotic activity with numerous inclusions (Fig. 18) In contrast the part of the nerve proximal to the lesion contained normal axons, myelin sheaths and Schwann cells (Fig. 19) Some fibres in the distal stump were better preserved than the others Most of the afferent nerve endings were disintegrated, those remaining being severely changed (Fig. 20). Efferent nerve fibres were still in contact with sensory cells, but at this stage vesicles were disintegrating and being replaced by a granular filamentous substance Even the mitochondria displayed evidence of degeneration. In places the subsynaptic sac showed a tendency to break up but this specific structure was highly irregular in shape even in the normal material (Fig. 21). The surface and the hairs of the sensory cells were usually intact but there was some increase in the amount of foreign material in the cell bodies. The supporting cells contained more definite accumulations of inclusion bodies. Even when the nerve endings had completely disappeared, there were still many synaptic bodies near the plasma membrane and these were surrounded by a few synaptic bodies.

5 and 6 days (2 animals). After simple transsection of ampullar nerves, some hair cells had very large irregular sensory hairs and protrusions of parts of the cuticle, although the configuration of the mitochondria ribosomes and cytoplasm in general was normal and the cells still had several intact synaptic bodies.

7 days (one animal) The sensory and supporting cells were essentially the same as those in the 2–3-day material without the changes in the cuticula and sensory hairs.

8 days (one animal) The cells in the crista had also a rather normal appearance in this specimen, but some accumulations of fine granular

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Fig. 20 Degenerated afferent nerve ending still in contact with sensory cell (3 d post-op.).
Fig. 21 Efferent nerve ending showing disintegration of vesicles and degeneration of mitochondria (3 d post-op.).
Fig. 22 Regenerating nerve fibres in sensory epithelium close to the basement membrane (7 d post-op.).
Fig. 23 Cross-section of a sensory hair bundle of denervated epithelium Normal structure (and normal structural polarization) (13 d post-op.).
Fig. 24 Presynaptic complex in relation to membrane close to a supporting cell. Horizontal crista, denervated (13 d post-op.).
Fig. 25 Regenerating nerve fibres in anterior crista epithelium (13 d post-op.).
Fig. 26. Synaptic body with vesicles and afferent nerve ending without normal synaptic structure (anterior crista, 13 d post-op.).
Fig. 27 Afferent synaptic complex formed after reinnervation (20 d post-op.).



Fig. 30–31. Two sections of an afferent nerve ending in synaptic contact with sensory cell. Note the accumulation of mitochondria in the ending and the large number of vesicles around the synaptic body (42 d post-op.).

13 days (one animal). When the horizontal ampullar nerve had been divided and transposed to the distal stump of the anterior vertical nerve, the horizontal crista had intact sensory cells with a normal surface, sensory hairs and kinocilia (Fig. 23). The sensory cells were apparently devoid of nerve endings in all sections and no nerve reached this crista. Some synaptic bodies were still attached to the plasma membrane: they were surrounded by a single layer of synaptic vesicles and often located in an area in which the sensory cells were in contact with supporting cells (Fig. 24). Thus, the open spaces formed by the degenerating nerve endings had disappeared at this stage.

Most of the foreign material accumulated in supporting sensory cells had also disappeared. To judge from the general appearance of the sensory epithelium, its reaction was less pronounced than a few days previously and it seemed that a certain amount of recovery had taken place.

In the anterior vertical crista, which was supplied by the branch from the horizontal nerve, a large number of regenerating nerve fibres were seen (Fig. 25). They reached the sensory cells and new nerve endings were found in contact with the synaptic area of the sensory cells, however, no complete synaptic structure could be identified (Fig. 26). In the majority of these nerve endings there was a very dense accumulation of mitochondria and sparse vesicles. No efferent fibres were identified.

15 days (one animal). After division of both ampullar nerves close to the bifurcation, nerve fibres were found below the epithelia but not inside them. In some sensory cells in the anterior

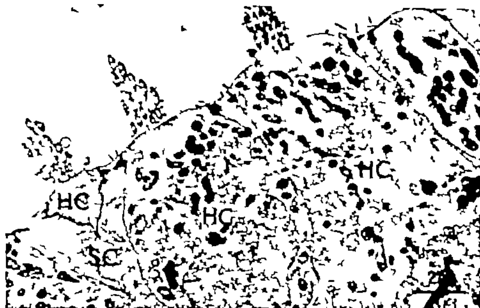


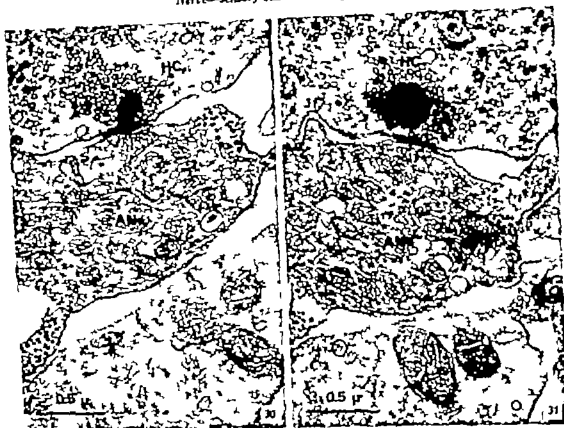
Fig. 28. Part of reinnervated crista with sensory and supporting cells of normal appearance (42 d post-op.).

material and the presence of a few cells with amoeboid protrusions in the endolymphatic space suggested an inflammatory reaction (there was also an increased amount of osmium-stained material in the perilymphatic linings seen at dissection).

Regenerative phase

A few regenerating nerve fibres were found in the basal part of the epithelium only *7 days* after transsection without transposition of the nerve (Fig. 22).

Fig. 29. Survey of basal part of crista with nerve terminals in contact with sensory cells (42 d post-op.).



Figs. 30–31. *Two sections of an afferent nerve ending in synaptic contact with sensory cell.* Note the accumulation of mitochondria in the ending and the large number of vesicles around the synaptic body (42 d post-op.).

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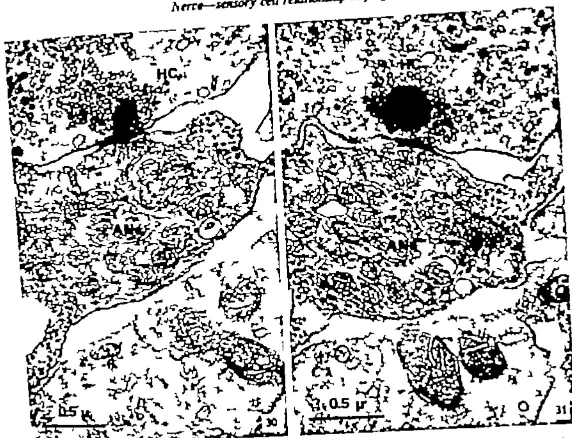
Fig. 28. Part of reinnervated crista with sensory and supporting cells of normal appearance (4 d post-op.).

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Fig. 3. Efferent nerve ending in synaptic contact with a sensory cell. The synaptic complex is normally differentiated (4. d post-op.).

crista cytoplasm was rather poorly structured with an increase in the number of small vacuoles, but the cells, including the synaptic bodies, were otherwise normal as described above. In the horizontal crista the cells had a normal structure.

20 days (one animal). The distal part of the nerve contained a mixture of a few apparently normal myelinated fibres, large numbers of unmyelinated nerve fibres, accumulations of degenerated myelin sheaths, and Schwann cells filled with degenerated material. The sensory epithelium was richly supplied with branching nerve terminals although some synaptic bodies still remained in contact with areas where sensory cells were attached directly to a supporting cell. Other synaptic bodies were found in the synaptic areas of newly formed nerve endings. From this stage on more or less complete afferent complexes were observed (Fig. 27). The nerve terminal now contained mitochondria of varying sizes, and vesicles, some of which were seen to have dense central cores.

28 days (one animal). The picture was essentially similar to the preceding specimen, while at *37 days (one animal)* one efferent nerve ending was found in synaptic contact with a sensory cell. In the latter specimen there were also a great many nerve fibres in various initial stages of myelinization, intermingled with bundles of unmyelinated fibres in the terminal parts of the regenerated nerve.

42 days (one animal). The electron microscopic survey of the reinnervated crista showed normal sensory cells (Fig. 28). The appearance and orientation of the sensory hair bundles were as in the normal frog. There were a large number of terminal nerve fibres between the basal parts of the cells of the crista (Fig. 29). The synaptic structure of afferent nerve endings in contact with the sensory cells was normal (Figs. 30, 31) and efferent nerve endings with a large accumulation of synaptic vesicles were found in the epithelium (Fig. 32). Besides the vesicles, the afferent nerve endings contained numerous mitochondria and some dense bodies. The contact between the afferent ending and the sensory cell was well established and the various structures of the synapse had formed. Some of the synaptic bodies were surrounded by large numbers of synaptic vesicles. Thus, although nerve fibres were still fewer than in the control material, those that had reached the epithelium had established normal morphological contact with the

sensory cells. The specimen fixed and prepared *after 46 days* was at essentially the same stage as that from the 42-day animal, however the poorer preservation of fine structure in the specimen precluded more detailed analysis.

Discussion

Object of Study and Methodological Problems

In the present study attention was focused on the structural relation between the nerve terminals and sensory cells during the interval between the division of the ampullar nerve and the restoration of functional and morphological organization.

The technical approach was limited to the part of the labyrinth containing the two rostral ampullar nerves and the related cristae. This afforded the possibility of selective elimination of the nervous supply to one crista, while the other could be used as a control—an advantage because of the variations in tissue fixation. In animals in which both ampullar nerves were divided and in most of the others, the controls were the posterior crista of the ipsilateral labyrinth and one or more of the contralateral cristae.

Even simple transection of the nerve may lead to damage (for instance anoxia, infection or toxic metabolites may result in changes in different parts of the specimen. In a few cases, division of major vessels was followed by rapid disintegration of the nerves and the sensory epithelia, but in most of the surviving animals the circulation was acceptable. When the division was performed distally to the common branch of the nerve there was minimal disturbance of the visible arterial capillaries along the nerve. In a few specimens, the nerve was cut further proximally but, because of microscopic evidence of a deterioration of the circulation, this method was abandoned.

During the preparation of the specimens for ultrastructural study there is also great danger of mechanical traumatization which may produce changes at the cellular level if the fixative has not penetrated the tissues adequately. In some cases, attempts were made to dissect the labyrinths carefully before fixation and place the anterior part of them in a fixative. On subsequent electron microscopy the same type of changes as described for one of the 24 h-specimens were found—some sensory cells had intensely swollen nuclei and vacuolization of the cytoplasm, others were normal or shrunken (and the tops of some cells were also ruptured, allowing extrusion of cytoplasmatic components into the endolympatic space). In fact, this particular specimen (and two others in the series) was dissected a little more brusquely than the others—the bony capsule was opened by means of a watchmaker's forceps instead of by drilling.

One aim of the present investigation was to examine the results of false innervation by transposing one nerve to the neighbouring crista. In the restricted area close to the crista where the nerve was divided the nerves were so short that the time for complete outgrowth was only about 2 weeks, thus, no examination of denervated epithelium over a longer period could be made in this study.

Gross Regeneration of Nerve Fibres

For comparison with the gross morphological pictures reported by Gribenski (1963), an attempt was made to follow the course of degeneration and regeneration of the nerves by inspecting the specimens *in vivo* and during the fixation and staining procedures. One essential difference between the methods is that whereas Gribenski destroyed the horizontal crista by cauterization in order to eliminate nerve contacts and impulses from the crista, in the present study an attempt was made to minimize the lesions so as to pre-

serve the normal ultrastructure. The regenerating fibres were seen to grow centrifugally from the two proximal nerve stumps and in a short time there was intermingling of their fibres. About 2 weeks postoperatively there was clear reinnervation of the vertical crista from the horizontal nerve. At the same time tests revealed a physiological response similar to Gribenski's "reaction R" thus corresponding in time with his findings. The regenerated fibres subsequently reached the two cristae from the horizontal nerve stump and fibres from the anterior nerve grew into the anterior crista. It was not clear whether the anterior nerve also contributed to the innervation of the horizontal crista.

Degeneration of Nerve Fibres and Terminals

The changes in axons and myelin sheaths after sectioning of the nerves do not differ from the pattern described by other workers (e.g. Glimstedt & Wohlfahrt 1960, Ohmu, 1962). However the myelin alterations seem to be comparatively rapid, probably due to the small distance between the lesions and the nerve terminals. No regular changes were found in the proximal stumps, other than in the immediate vicinity of the lesions, but signs of retrograde degeneration were not systematically looked for. The pattern of degeneration in the nerve terminals has received considerably more attention in the literature, especially in connection with the experiments on selective destruction in the central nervous system, where identification of the degenerating fibres in based on changes interpreted as evidence of degeneration.

Three types of anterograde degenerative changes in nerve endings in the central nervous system have been described. The first is characterized by a striking initial increase in the number of neurofilaments, accompanied by swelling of the damaged process and followed by shrinkage of the profile and considerable increase in electron density. The second type consists of an increase in the electron density of the axoplasm with no loss of synaptic vesicles and little alteration in the size and shape of the terminal. The third type has been referred to as electron-lucent or "pale" degeneration due to its lack of axoplasmic electron-density and apparent loss of synaptic vesicles (Raisman & Matthews, 1972, O'Neal & Westrum 1973, Gentschev & Sotelo, 1973). The interrelationships between these types of degenerative change do not seem to be quite clear and there are variations according to the species studied, the age of the animal and the system chosen for study. The heterogeneity of degenerative patterns is greater in the peripheral nervous system than in the CNS and the reaction of the terminals in peripheral sites is more rapid than in the central ones (Raisman & Matthews 1972). Apparently there are also variations between different specimens due to variations in the preparative and fixative procedures used. The main problem in the present study was not to separate undegenerated terminals and terminals of similar type in various stages of degeneration in order to trace a distinct tract, but to follow the changes in time in a limited series of animals. The asynchronism of degeneration may result in disappearance of many terminals while others of an identical type may appear to be little changed. Hillman (1969) showed that all efferent nerve endings in the labyrinth of the frog do not degenerate at the same rate.

Two days after dividing the crossed olivocochlear bundle in guinea pig, Kimura & Wersäll (1962) found alterations in the large efferent endings of the cochlea, with an increase in the density of the synaptic vesicles in the terminals, followed by degeneration of mitochondria and complete degeneration of the nerve endings 5 days after division. Transsection of the cochlear nerve in the internal auditory meatus led to degeneration of the efferent and more slowly of the afferent nerve endings. The later degeneration of the afferent terminals was ascribed to a survival of the ganglion cells for a time after division of the nerve. Iurato (1962) reported changes in the efferent endings in the rat as early as 16 hours after sectioning of the olivo-cochlear bundle. Smith & Rasmussen (1963) showed regressive changes in the large nerve endings on the outer hair cells in the

cochlea of the chincilla 3 days after cutting the olivo-cochlear bundle. Débris of the endings were found after as much as 32 days. The same authors reported (1968) degeneration of efferent *nerve endings* in the vestibule 6–8 days after dividing the efferent nerve bundles in the medulla. After sectioning the olivo-cochlear bundle in the internal acoustic meatus, Spoendlin (1966) found distinct signs of degeneration of the large vesiculated endings in cat after one week. He has later (1971) shown that the apparent persistence of innervation in the organ of Corti after sectioning the cochlear nerve is to be ascribed to the survival of a small number of cells in the spiral ganglion, which send their axons to both the outer and the inner hair cells and which resist retrograde degeneration. Remarkably rapid degeneration of the efferent nerve endings was found by Hillman (1969) after cutting the vestibular nerve and brain stem in *frog. He presented pictures* of dense masses formed from degenerated efferent nerve endings within 2 days after the lesion. This type of change was *not found* in the present material where rather well preserved endings were found *even after* 3 days. It is, however obvious that a large number of nerve endings had disappeared at this stage. Hillman also noted that many of the efferent fibres were lost *already* after 2 days. This should be compared with the report by Robbins et al. (1967) that a rather small number of *efferent fibres was found in* the nerve branches to the sensory epithelia 2–3 weeks after cutting the vestibular nerve.

In the present material the marked changes in the distal stump of the nerve and in the afferent endings shortly after division may be due *to an* increase in the permeability of capillaries in the nerve, as was shown in peripheral nerves by Mellick & Cavanagh (1968) and also discussed by *Berger (1971).* During the next 24–48 hours there was progressive degeneration. In contrast to these consistent changes *in the afferent* nerve endings, there was no sign of *changes* in the efferent endings after 2 days. On the *third day* disintegration of the vesicles was evident. This *difference in* the time course of the degenerative changes in the efferent and afferent nerve endings in a particular end organ specimen may be due to a higher rate of metabolism in the afferent nerves and nerve endings than in the efferent ones. In the specimens there are no efferent action potentials in the distal stump, and no transmission in the efferent synapses, which implies a reduction in the consumption of energy. The transmission in the afferent synapses and nerves is essentially unchanged (Glesner & Henriksson, 1964) or possibly increased owing to loss of the inhibitory effect of the efferents, as was shown in *frog* by *Llinás & Precht (1969)* and by Goetmakers & Groen (1970). Thus, the metabolic demand is not reduced in afferents and when energy-rich substrates cannot be supplied from the cell body by normal axonal proximo-distal *transport thus may lead to a* more rapid degeneration than in the efferents. This explanation might imply that some substances are involved in the maintenance of both structural and functional integrity and may be related to the *fast component of* transport in axons, shown by Ochs (1972) to utilize ATP and also thought to be responsible for *supplying materials* specifically required at the synaptic terminals (Grafstein, 1969).

Regenerating Nerve Fibres

During the regenerative phase, afferent nerve endings were found long before efferent ones. This may be *due* to the fact that the distance between the efferent nerve cell-body and the end organ is greater than that between the afferent nerve cell-body and the end organ, provided that the growing tip of the proximal stump is dependent on newly synthesized materials carried *from the cell* body by means of the slow component of axoplasmic transport.

The fact that those parts of the synapses which *belonged to the hair* cell (synaptic body, vesicles, end-foot and membrane) were *often* intact *during the denervated stage* suggests that the synapses in regenerated specimens are really *original synaptic points.* The possibility that *de novo* contacts develop between nerve endings

serve the normal ultrastructure. The regenerating fibres were seen to grow centrifugally from the two proximal nerve stumps, and in a short time there was intermingling of their fibres. About 2 weeks postoperatively there was clear reinnervation of the vertical crista from the horizontal nerve. At the same time tests revealed a physiological respons, similar to Gribenski's "reaction R" thus corresponding in time with his findings. The regenerated fibres subsequently reached the two cristae from the horizontal nerve stump and fibres from the anterior nerve grew into the anterior crista. It was not clear whether the anterior nerve also contributed to the innervation of the horizontal crista.

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Three types of anterograde degenerative changes in nerve endings in the central nervous system have been described. The first is characterized by a striking initial increase in the number of neurofilaments, accompanied by swelling of the damaged process and followed by shrinkage of the profile and considerable increase in electron density. The second type consists of an increase in the electron density of the axoplasm with no loss of synaptic vesicles and little alteration in the size and shape of the terminal. The third type has been referred to as electron-lucent or "pale" degeneration due to its lack of axoplasmic electron-density and apparent loss of synaptic vesicles (Raisman & Matthews, 1972, O'Neal & Westrum, 1973, Gentschev & Sotelo, 1973). The interrelationships between these types of degenerative change do not seem to be quite clear and there are variations according to the species studied, the age of the animal and the system chosen for study. The heterogeneity of degenerative patterns is greater in the peripheral nervous system than in the CNS and the reaction of the terminals in peripheral sites is more rapid than in the central ones (Raisman & Matthews 1972). Apparently there are also variations between different specimens due to variations in the preparative and fixative procedures used. The main problem in the present study was not to separate undegenerated terminals and terminals of similar type in various stages of degeneration in order to trace a distinct tract, but to follow the changes in time in a limited series of animals. The asynchronism of degeneration may result in disappearance of many terminals while others of an identical type may appear to be little changed. Hillman (1969) showed that all efferent nerve endings in the labyrinth of the frog do not degenerate at the same rate.

Two days after dividing the crossed olivocochlear bundle in guinea pig, Kimura & Wersäll (1962) found alterations in the large efferent endings of the cochlea, with an increase in the density of the synaptic vesicles in the terminals, followed by degeneration of mitochondria and complete degeneration of the nerve endings 5 days after division. Transsection of the cochlear nerve in the internal auditory meatus led to degeneration of the efferent and, more slowly, of the afferent nerve endings. The later degeneration of the afferent terminals was ascribed to a survival of the ganglion cells for a time after division of the nerve. Iurato (1962) reported changes in the efferent endings in the rat as early as 16 hours after sectioning of the olivo-cochlear bundle. Smith & Rasmussen (1963) showed regressive changes in the large nerve endings on the outer hair cells in the

with signs of degeneration or derangement of the morphological polarization after denervation. In the case of some other secondary organs, degenerative processes which proceed differently have been described in the receptor cells. Thus, in fishes and mammals, taste buds gradually degenerate and disappear in a relatively short time after denervation, often within 1–2 weeks (reviews by e.g. Zelená, 1964 Jeppson, 1969). An exceptionally slow degeneration of taste cells in the frog was noted by Robbins (1967) this has been related to the special morphological characteristics of the cells in that species (Guth, 1971). Lateral-line organ sensory cells degenerate rapidly in fish but after varying periods of time in amphibia where according to Jones & Singer (1969), the first changes in the adult newt appear within 3 weeks after elimination of both the lateral-line and the spinal nerves, leading to advanced degeneration within 2 months. However the earlier much debated, but generally accepted, theory of a dependence of sensory cells on nervous connections in terms of a trophic influence, leading to total elimination of the cells after a prolonged period of nerve deprivation seems, in certain respects to be contradicted by the findings of Flock et al. (1973) They observed autonomous differentiation and normal morphological polarization of hair cells of salamander tadpoles devoid of innervating nerve endings. Certain specialized lateral-line organs, namely electroreceptors, such as the tuberous organ of mormyrid fish, degenerate in 2–12 days after denervation (Roth & Szabo, 1969), and rapid changes have been described in the sensory cells of the ampullary organ of catfish (Szamier & Bennet, 1973) and the ampullae of Lorenzini of electric ray (Derbin, 1970) where the presynaptic rods are changed within 6–12 hours and 3–4 day respectively after nerve section signs of cytoplasmatic degeneration appearing later in these cells.

The persistence of the sensory cells in the organ of Corti after sectioning of the cochlear nerve as reported by Spoendlin & Gacek (1963) and others is probably not a conclusive sign that hair cells are independent of nervous contacts, as nerve terminals have been found in the organ such endings probably belong to surviving cells in the spiral ganglion (Spoendlin, 1971).

Vestibular sensory cells have been reported to degenerate after cutting the ampullar nerves in squirrel monkeys (Igarashi & Miyata, 1972), but similar results in cats were interpreted by Mair & Fernández (1966) as being caused by nervous ischemia this was corroborated by Silverstein & Makimoto (1973) who found no light microscopical signs of vestibular cell degeneration in cat when the vessels were intact at nerve sectioning. Gribenski (1963) showed advanced degeneration of the ampullar crista in the frog 4 weeks after nerve division, provided regeneration was prevented ("e.g. by destruction of the ganglion of Scarpa"), but the degree of vascular interference in those preparations was not described. Our pilot experiments in which the nerve was cut proximal to the utricular branch resulted in an obvious decrease in the peripheral circulation, and in rapid degeneration in the sensory epithelia. Following careful peripheral cutting as described above, we found only *rare examples of* sensory cell alterations, no evidence of total cell degeneration and no signs of breaking of the presynaptic afferent complex in a denervated stage However it is *quite* possible that a more pronounced degeneration would have taken place if the epithelium had been deprived of nervous connections for longer periods than 1–2 weeks.

At the denervated stage, efferent postsynaptic structures could not be identified in the hair cells. Elongated spaces with a limiting membrane could be seen in the basal parts in the proximity of the sensory cell wall, but such structures, without relations to nerve endings were also sometimes found in normal sensory cells. Thus, it was not possible to exclude some loss of structural integrity of the efferent postsynaptic sites, as was shown by Kimura & Wersäll (1962) in the organ of Corti of the guinea pig. In the sympathetic ganglion cells of the frog there are however no signs of transsynaptic changes after denervation (Sotelo, 1968). There are also many examples of persistence of postsynaptic speciali-

and cells during the regenerative phase cannot however be ruled out

When hair cells in the lateral line canal organ of salamander tadpoles are studied *in vivo* synaptic bodies can be seen to change their positions, and during differentiation of epithelial cells into hair cells in denervated preparations synaptic bodies are found freely distributed in the cytoplasm (Flock et al 1973) This might imply a plasticity of afferent presynaptic sites also in developed hair cells during denervated stages which is however difficult to see in ordinary sections The existence of synaptic bodies surrounded by vesicles without close contact with the cell membrane has, however in some instances been confirmed by us in operated animals studied by serial sectioning.

The marked specificity in a regenerating nerve fibre to reestablish contact with the end organ or neuron to which it was originally connected, has been ascribed to specific biochemical characteristics of the neuron, which are determined by developmental processes early in differentiation Examples of the reestablishment of specific connections are provided by retinal cells and the optic tectum (Sperry 1963 Jacobson 1968) It is, however possible for a nerve to make contact with another neuron or another end organ, within certain limits (sensory nerves do not form functional connections with muscles, and motor nerves do not innervate sensory organs) The new inappropriate contact is then promoted if not actually made possible by denervation of the organ to be contacted (Sperry & Arora 1965) This was also observed when the horizontal ampullar nerve reinnervated the anterior crista in the frog, producing synaptic structures of normal appearance but with a tendency for misdirection of vestibular reflexes

At a later stage fibres from the same nerve grew further to the horizontal crista. The 'false innervation stage' was possible only a transitory phase before there was complete reorganization of the original contacts, as no obstacle to this process was provided (cf Sperry 1945) On the basis of the present material it has not been possible to establish whether or not the transposed fibres from the horizontal nerve remain in contact with the sensory cells of the anterior crista. However no degenerating nerve endings were found in the sensory epithelia which were reinnervated by any of the nerves. An interesting observation was made by Marotte & Mark (1970*a* *b*) and Mark et al. (1972) who noted persistence of ultrastructurally normal synaptic endings on the eye muscles of fish after cross unions of oculomotor nerves, which first resulted in movements controlled by the newly (inappropriate) innervating nerves, but after regeneration of the proper nerves the muscles regained their normal functions apparantly the synaptic functions of the improper nerve endings had been blocked or the muscles had been insensitive to transmitter when their original nervous contacts had been reestablished No signs of degeneration of the endings which arrived first could be found The result point to the possibility that selective mechanisms are involved in the developmental patterning of synaptic connections and that they also influence the efficiency of transmission at formed synaptic complexes.

There is strong evidence that specificity of peripheral sensory and motor neurons is mediated from their peripheral connections In early developmental stages the central synaptic associations are specified by means of biochemical mechanisms. In these early stages it seems to be possible to change central connections, as in the case of respecification of cutaneous nerves after transplanting skin from the back to the belly of frog tadpoles, resulting in misdirected reflexes after metamorphosis, (Jacobson & Baker 1969). Whether central synaptic reorganization is possible later in ontogeny or in higher animals is less certain only few indications of such a plasticity have been reported (see Jacobsson 1971 Cragg, 1972)

Sensory Cells after Denervation

One aim of the present experiments was to find out whether the sensory cells of the crista reacted

Concluding Remarks

On the basis of the observations made in this study it would appear that sensory cells in the labyrinth survive total denervation for a short period without regular signs of ultrastructural damage. Moreover afferent synaptic structures in these cells are often preserved in the denervated stage, and afferent and efferent nerves reinnervate the vestibular epithelium after division of the ampullar nerve. The afferent nerves degenerate and regenerate earlier than the efferent ones. The nerve fibres from horizontal ampullar nerves can innervate a denervated anterior vertical crista, but this results in misdirected reflexes. The initiation of morphological and functional normalization becomes evident about one month after division of the nerve.

Summary

The degeneration and regeneration of afferent and efferent nerves to the crista ampullaris in the frog were studied after transection of the ampullar nerves. In some experiments one or both rostral ampullar nerves were simply divided and left in place. In other experiments the ampullar nerves to the horizontal and to the anterior vertical crista were divided and the branch to the former was brought into contact with the distal stump of the anterior vertical ampullar nerve.

Sensory cells in the labyrinth survived total denervation for 1–2 weeks without regular signs of ultrastructural damage. The afferent synaptic structures in these cells were often preserved in the denervated stage. The afferent nerve fibres degenerated earlier than the efferent ones. Both type of fibres reinnervated the vestibular epithelium after division of the ampullar nerve. The fibres from a horizontal ampullar nerve could reinnervate a denervated anterior vertical crista, resulting in misdirected reflexes. About 40 days after division both function and morphological organization had been restored to normal.

Zusammenfassung

Entartung und Regeneration afferenter und efferenter Nerven der Crista ampullaris beim Frosch wurden nach Durchtrennung der Ampullennerven untersucht. Bei einigen Versuchen wurden einer oder beide rostrale Ampullennerven einfach durchtrennt und dabei gelassen. Bei anderen Experimenten wurden die Ampullennerven der horizontalen Crista wie auch der Crista anterior durchtrennt und danach der Ast der horizontalen Crista mit dem distalen Stumpf des N. ampullaris anterior anastomosiert.

Es wurde beobachtet, dass die Sinneszellen des Labyrinthes bei totaler Denervation ohne regelmässige Zeichen einer ultrastrukturellen Schädigung 1–2 Wochen überleben können. Die afferenten synaptischen Strukturen in diesen Zellen bleiben auch im Stadium der Denervierung oft erhalten. Die afferenten Nervenfasern degenerieren früher als die efferenten. Die afferenten wie auch die efferenten Nervenfasern besorgen die Reinnervation des vestibulären Epithels nach Durchtrennung des Ampullennerven. Die Nervenfasern eines horizontalen Ampullen-

zations after deafferentiation in the central nervous system they were often apposed by various elements (Pinching, 1969 O'Neal & Westrum 1973)

Relation between Morphology and Physiology

The misdirected vestibular reflexes elicited by impulses from the anterior crista to the horizontal nerve have been described by Gribenski (1963) who discussed the possibility of two types of nerve fibres in each ampullar nerve, one which takes part mainly in the tonic function of the labyrinth and another which participates especially during the stimulation produced by the flow of endolymph Electrophysiological studies using single fibre recordings have shown that there are two principal groups of afferent fibre activity from the horizontal ampulla of the frog a small proportion show little or no adaptation on prolonged acceleration and are characterized by a rather regular resting activity while most fibres show a marked adaptation on stimulation and irregular frequency at rest. However all fibres in the horizontal nerve show an increase in frequency on utriculopetal deviations of the cupula (Flock & Gleisner 1968 cf Precht et al. 1971 Goldberg & Fernandez, 1971 *a b*) The so-called tonic function of the ampulla should rather be discussed in terms of the mere existence of nervous activity which gives a balanced input to the central connections in the animal from both labyrinths under resting conditions. The fact that an inappropriately reinnervated anterior vertical crista preserves its original morphological polarization after establishment of ultrastructurally qualitatively normal synaptic contacts of the afferent type implies that an increase in afferent nervous activity occurs on utriculofugal cupula deviation in the ampulla The presence of misdirected reflexes is in good accordance with the view that the central connections do not change within the time of reinnervation The initial phase of normalization of responses to tilting and rotatory stimuli after about 3–4 weeks in our material might be ascribed to the structural peripheral reorganization towards normal conditions as already discussed There is also the possibility that after regeneration of efferent terminals an increased degree of efferent feedback contributes to an inhibition of inappropriate input at a stage when this peripheral reorganization has not taken place. Electrophysiological correlations of the behavioural responses and the morphological findings in the present type of experiment on the vestibular apparatus are not known to the authors. Furthermore the improvement of vestibular reflexes after peripheral lesions is known to be due to compensation at the level of the vestibular nuclei after partial or complete loss of normal input of nerve impulses from the labyrinth as has been shown by Precht et al. (1969) and McCabe et al (1972) Gribenski noted that the frogs which exhibited a reaction "R had a reduced response to horizontal rotatory stimuli compared with animals simply deprived of one horizontal crista about one month after the respective operations A possible clue to the explanation of this result is the finding by Caston & Gribenski (1972) that the activity in most fibres of the intact anterior vertical ampullar nerve decreased on rotatory acceleration in the horizontal plane which causes increased activity in the horizontal nerve of the same side This would give a simultaneous increase (or decrease) in the two horizontal nerves on testing the R frogs, resulting in a diminution of the differential input to the nuclei Since we did not perform any quantitative measurements of those responses we were unable to confirm this finding.

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nerven können eine Crista anterior innervieren die denerviert wurde und funktionelle Fehlreaktionen verursacht. Morphologisch wie auch funktionell ist zirka 40 Tage nach dem Eingriff völlige Normalisierung erreicht.

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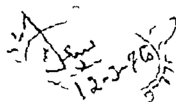
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F BRACCHI T GUALTIEROTTI [1]
A MORABITO and E ROCCA

From the II Physiological Department,
University of Milan Medical School, 20133 Milano,
Via Mangiagalli, 32, Italy

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OFO-A Experiment principal investigator

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Introduction

On November 9 1970 two bull frogs were successfully injected into earth orbit by means of a four stage Scout rocket assembly launched from the NASA launching site on Wallops Island Virginia, USA They were housed in a satellite housing a Frog Orbital Experimental Package (FOEP) totally immersed in oxygenated water and serviced by an automatically controlled life support system. Also included in the package was a centrifuge and the electronic equipment necessary for telemetered transmission of signals encoding the amplified action potentials from selected otolith-controlled axons of the vestibular branches of the labyrinths the electrocardiogram of each frog the output of the centrifuge accelerometer and a time signal as well as various engineering data. A tape recorder accumulated data which were collected by 6 telemetry stations around the world which received and relayed the stored data on overflight.

An internal report of the technical and biological aspects of the mission has been submitted to NASA (Gualtierotti Bracchi & Rocca 197?) This report also contains a preliminary assessment of the results available at that time

The rationale underlying this bioprobe experiment was to study the effects of "free fall" or "weightlessness on a sense organ specifically evolved to respond to changes of the orientation of the animal's head within the earth-gravitational field of 1 g What, if any changes would be observed in the basic activity of the organ and in its mode of response to imposed linear acceleration in orbital flight $(10^{-4}-10^{-}$ g max.)?

In this mission transmission of data was monitored from space for six days which was the expected maximum period of proper functioning of the electric storage batteries supplying the life support and monitoring systems

The computer analysis of the wealth of telemetered data as well as of the data obtained from the preparations before the flight has now progressed far enough to allow of a comparative interpretation in terms of vestibular physiology of the recorded behaviour of four otolith-controlled units on the ground and in orbit both at rest and when exposed to centripetal acceleration by means of various schedules of standard centrifuge cycles programmed in advance and automatically executed during the flight

SUMMARY OF METHODS

In view of the inaccessibility of the internal NASA report, it will be necessary to summarize the most important points of method The selection of frogs the viability tests and the various stages of the operative procedure before the implantation of the "neutral buoyancy electrodes (Gualtierotti & Bailey 1968) as well as the implantation and instrumentation of these electrodes have been described by Gualtierotti & Gerathewohl (1965) and Gualtierotti & Alltucker (1966) in connection with experiments on the effect of "free fall" on otolith organs of the bull frog in parabolic flight. Since then all these techniques were further refined in preparation for the orbital flight experiment to be dealt with in the present paper

Essential points of these methods may be summarized as follows

1 The neutral buoyancy electrode is essentially a tungsten microelectrode sharpened with the technique developed by Hubel (1957). It has an attachment of polyethylene

ture maintained when in space within the range of 17°C±1.5°C The gas circulation system is filled with pure O_2 supplied by an O_2 bottle through a demand regulator the gas exchange takes place through an especially designed lung providing a large surface by means of several sheets of thin silicon rubber These are highly permeable to O_2 CO_2 and water vapour

The CO_2 is eliminated from the gas by absorption through a bed of barium hydroxide The circulation of the gas and water system is assured by two small pumps. The container for the biological preparations through which the water circulates passing through a filter system covering its entire walls forms the arm of a centrifuge that provides if needed angular and centripetal acceleration at the sites of the labyrinths of the two frogs placed tail to tail

The pressures in the gas and water compartments are equalized by an accumulator system This consists of a container with 2 chambers divided by a collapsible partition set to insure equilibrium of the pressures between gas and water

The appropriate water temperature is maintained by a thermostat and a heat exchanger The cooling is achieved by evaporation into the space vacuum and the heating by an appropriate heater The temperature control was manually operated not automatic but capable of being operated by telemetry In pre-flight on the ground cool air is pumped over the FOEP as the cooling system could not function in the atmosphere

During extended experiments carried out on the ground the FOEP was placed in a thermoregulated room The water temperature and pressure were controlled continuously

The biological signal was recorded through an emitter-follower (Gualtierotti & Gerathewohl 1965) which was connected to the frog s jaw and the signal was amplified by the main amplifiers to the voltage level appropriate for telemetry

The FOEP was encased in an air-tight canister containing air at the pressure of 1 atm both during the flight and on the ground

TELEMETRY

An appropriate telemetry system with a frequency response up to 2000 Hz was especially provided in the spacecraft to transmit the vestibular pulses

Data transmitted through the entire system included vestibular activity (four channels) ECG (two channels) the centrifuge accelerometer output water temperature casing pressure water pressure

PREPARATION FOR THE FLIGHT

As the main problem was precise timing and there was a need for being ready for a repeat mission in case of failure with a minimum turn-round time a group of 24 frogs were prepared with the purpose of having at least six of them ready at any given time

As the animals were kept in O_2 saturated water the frogs were already partially saturated with O_2 and this decreased the flushing time of the FOEP after the animals were placed into it (see below)

Twelve hours before transportation to the launching pad two of the frogs were placed in the FOEP The gas system of the FOEP was then flushed through an open loop oxygen circuit to dispose of the residual nitrogen in the frogs and in the water that might have accumulated during the handling of the package and of the resulting bubbles of air the presence of nitrogen in fact would have decreased the PO_2 in the gas circuit the capacity of which was limited

Periodical samples of centrifuge water were tested for oxygen content. The open oxygen loop was maintained till the PO_2 reached approximately 700 mmHg. The loop was then closed and the system supplied by the FOEP oxygen bottle through a demand valve that

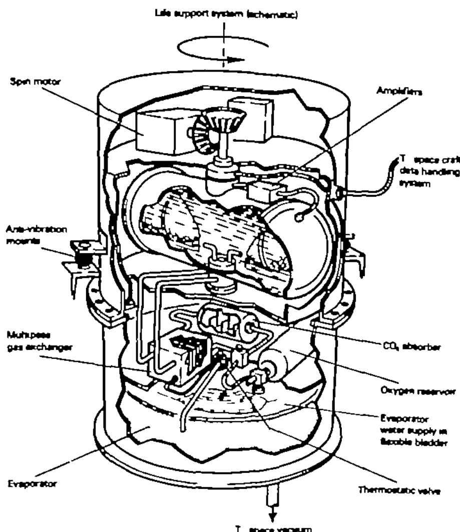


Fig 1 Schematic drawing of the FOEP (Frog Otolith Experiment Package) The life support system is shown including the gas exchanger (O_2–CO_2) the CO_2 absorber (Bariumhydroxide) the oxygen reservoir with a demand valve The two shapes drawn opposite the outlets of the gas exchanger pipes symbolize the position of the two frogs in the water-filled container Further description in the text

microtube containing an air bubble serving to equate the total density of the electrode with the density of the tissue in which it is to be embedded This makes the electrode nerve contact immune against the effect of the high g forces on blast-off (10 g thrust acceleration) and 2–600 Hz sinusoidal vibration at 1 g The successful recording from implanted vestibular units for a period of six days after injection into orbit bears witness to the excellent quality and reliability of this type of neutral-buoyancy electrode

2 The normal appearance of the ECG monitored during the entire mission in one frog and for 40 hours in the other shows that as on the ground the immersion in water of a PO_2 temperature ratio of 700 mmHg/16 5–17.5°C maintained the frogs in a state of physiologically adequate skin respiration compatible with normal activity of neuro-sensory systems

THE FOEP AND LOADING PROCEDURE

The FOEP or Frog Orbital Experiment Package is a compact unit (Fig 1) composed of three different systems A life-support system divided into water and gas circulation which assures a water environment with the appropriate filtered flow (300 ml per minute) a PO_2 between 650–700 mmHg and a tempera-

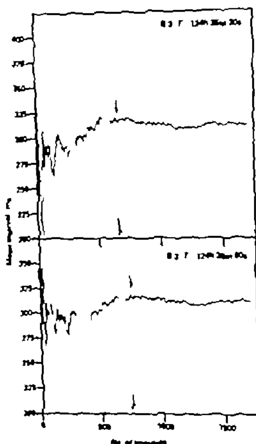


Fig. 3. Determination of the statistically significant sample by means of the sequential mean of the interspike intervals. At the arrow the curve becomes flat and parallel to the abscissa corresponding to 750 intervals approximately. This is empirically taken as significant sample. The bottom record is equivalent to the upper one but the sampling started 30 later.

the nearest receiving station edited and analysed through a Univac computer to provide a more limited program (e.g. acceleration profile time history and mean interspike interval).

It is obvious that visual inspection on the original analogue tapes is not feasible in long experiments of this sort in which hundreds of thousands of data are involved. The following technique was, therefore, used (Fig. 2). During tape editing the first impulse triggered a square pulse of 0.5 msec and the time base. These were continuously recorded on a storage oscilloscope. The spike immediately following would appear at a given time after the first. In this way the interval between the consecutive spikes was immediately evident and any pulse that happened to occur within the minimum interval typical of the unit (3 to 6 msec) would indicate either an artifact or an additional biological signal. Such a technique has the advantage that the entire series of data can be run continuously with an immediate possibility of checking any unwanted event. This technique facilitated the following procedures.

(*a*) Identification of bursts of noise and artifacts due to frog movements, telemetry gaps and any other superimposed event. The timing of such events or noise was noted through the time code recorded on a separate channel of the magnetic tape and the computer was instructed to ignore data recorded within the identified period of artifacts.

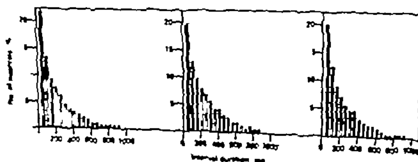


Fig. 4. Using minimum sample as determined by the method shown in Fig. 3, the interspike-interval distribution is studied by means of interspike-interval histograms of three different samples. They are very similar. The sampling technique therefore is considered to be correct.

maintained the required pressure The water PO_2 was tested again and this procedure repeated several times till the PO_2 was maintained at slightly above 700 mmHg The FOEP was then ready to be placed into its cannister This having been done ground control data were acquired and stored on magnetic tape Such data were

1 20 minutes of activity of the four vestibular units at rest

2 A number of single centrifuge spin cycles several minutes apart

3 A number of quadruple cycles during which the centrifuge was restarted as soon as it stopped

4 30 additional minutes of data immediately following the last centrifuge cycle

DESCRIPTION OF MISSION

During the entire period preceding the lift off the activity of the four vestibular units and the ECG of the two frogs were tested periodically through telemetry The data were recorded on a strip chart and on magnetic tape Starting approximately from 10 min before the lift off data were recorded continuously and the recording was carried out without interruption through the entire lift off up to injection in orbit till the time at which the satellite disappeared beyond the horizon outside the reach of the ground recording antenna No data could be obtained during the first orbit (90 min) owing to a command failure which was rectified from the second orbit onward

Data Handling and Analysis

All data (vestibular ECG time code and accelerometer) were transferred to digital magnetic discs by an IBM 1800 computer The time code (hour–minute–seconds) was memorized second by second along with biological data and constituted the main reference for data retrieval During A/D conversion the main code was used also to instruct the computer through punched cards to disregard all the periods where noise of any source (telemetry gaps muscular noise) was detected Different programs were developed to provide for

1	Sample duration	sec
2	Number of impulses	No
3	Impulse frequency	impulses/sec
4	Mean interval	msec
5	Standard deviation	σ
6	Variation coefficient	CV
7	Max interval	msec
8	Minim interval	msec
9	Range	msec

10 Histograms of different classes

11 Time history (on XY plotter) (*a*) Steady state data (*b*) Acceleration profile

During the orbital experiment it had to be decided within a few hours which experimental routine was to be followed next depending upon the behaviour of the vestibular units For this purpose data were collected directly from



Fig 2 Identification of the minimum impulse interval from continuously running data tape for the purpose of confirmation of true single-unit recording Each impulse triggers a 0.5 ms square wave The first impulse starts the time base of a storage oscilloscope If the activity of one unit only is recorded significant gap will follow the triggering impulse in this case of approx 5 ms If more than one unit is present no such gap will appear as the intervening signal will fill up entirely the time after the first triggering impulse This method allows continuous identification of any number of impulses belonging t single unit

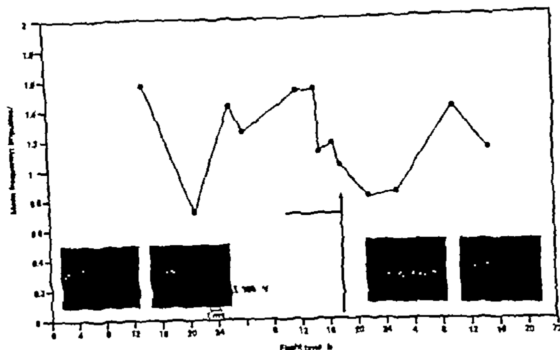


Fig. 5. Effects of slow ... of oxygen tension up to 1.7 atm in the FOLP ... on the firing rate and configuration of action potentials of ... statoreceptor unit. The arrow indicates the end of the ... pressure after 8 hours. Water temperature 16.5–17 °C. Ordinate: Mean frequency of 2000 impulses for each point. Abscissa: Duration of ... periment in hours. Inserts: Sample of impulses before (left) and after pressurization (right).

All conditions and test procedures were the same with the exception of the existence of the earth-gravitational field of 1 g. 5 units were studied for 170 hours recording at 1 hours intervals during day and night. After the successful flight four additional units were studied for 48 hours with recordings made for 15 min every 45 min.

The receptors were identified as tonic statoreceptors when they showed a response significantly representative of the different steady-state spatial positions of the head (t



Fig. 4. ECG (ordinate on right) and statoreceptor firing rate (... dinate on left) during 48 hours of recording on the ground. The frog was kept at ... ater temperature of 1... 0 °C. The unit responded throughout the experiment to just above threshold vibration of the ... ater pump (for detail see text). Recording every 15 minutes in the hour. Mean and standard deviation both for ECG (black lozenges) and discharge frequency (empty triangles) (... 000 impulses for each point).

(*b*) Adjustment of a clipping level in order to make sure that no additional unwanted biolog ical signal might be computed For biphasic potentials with a sizeable second phase opposite to the main pulse a double clipping tech nique was used

With a large amount of spike train data the *chief problem was to determine a statistically* significant sample This is very difficult and a satisfactory solution has not been found The calculation of the sequential means was used for this purpose (Fig 3) *Alternatively the* interspike interval distribution could be evaluated by means of interspike interval histograms in different samples of the same number of events (Fig 4) For a steady state activity (no trend detected) the distribution appeared to be closely the same and the cor *responding number of intervals* were taken as being sufficient for a statistically significant sample

Results

ASSESSMENT OF THE FROG S CONDITION UNDER WATER IN THE FOEP O_2 CONSUMPTION

A frog of known weight and prepared as for the flight except for the chronic microelectrodes implantation was placed in the FOEP kept at various constant temperatures (between 10° and 25°C) to measure the oxygen consumption as a function of the environ mental PO_2 in the bath water changing it from 700 to 400 mmHg in steps

When the limbs were paralyzed by cutting the branches of the sacral and thoracic plex uses there was normal consumption of ox ygen (160–180 ml O_2 h/kg) at a PO_2 of between 600 and 700 mmHg in the environmental water at a temperature of 16 5–17 54°C These para meters are identical with those maintained during the orbital flight Below 500 mmHg and especially on a sharp decrease over the range between 550 and 500 mmHg the oxygen con sumption decreased to an average of 30 ml/h/kg Distress symptoms became evident after approximately two hours signalled by an increase of the amplitude and duration of the T wave of the ECG In this condition the frog survives for some hours only

The ambient temperature is critical Changes towards the lower and upper limits of the above mentioned range produce irregular ity of the heart rate and changes in the am plitude and duration of the R waves Most of these changes are reversible but recovery may take many hours

At nearly 1 atm of PO_2 oxygen poisoning *might be expected to take place during* an ex posure of several days

That this does in fact not occur was de monstrated by increasing the PO_2 in the FOEP to 1 7 atm and comparing the ECG as well as the amplitude and shape of the vestibular ac tion potentials and the firing rate at normal and increased O_2 pressure for 3–5 days No effects were found (Fig 5) and the O_2 consumption remained unaltered

THE ACTIVITY OF THE VESTIBULAR STATORECEPTORS

A On the ground (1 g)

The activity of single statoreceptors (20 units) of the labyrinth of the bull frog in air studied for 10–48 hours has been described elsewhere (Gualtierotti 1968) In the present paper the description will be limited to the impulse train data recorded from single vestibular nerve fibres activated by statoreceptors in frogs kept under water within the FOEP This apparatus is identical to the one which was used for the investigation of the effect of "weightlessness during the 6 1/2 days orbital flight of the OFO A experiment

Fig. 5. Effect of slow rise of oxygen tension up t[illegible] 1.7 [illegible] in the FOEP water on the firing rate and configuration of action potentials of [illegible] statoreceptor unit. The arrow indicates the end of the rise in pressure after 8 hours. Water temperature 16.5–17.2°C. Ordinate: Mean frequency of [illegible]000 impulses for each point. Abscissa: Duration of experiment in hours. Insert: Sample of [illegible] impulses before (left) and after pressurization (right).

All conditions and test procedures were the same with the exception of the existence of the earth-gravitational field of 1 g. 5 units were studied for 170 hours recording at 12 hours intervals during day and night. After the successful flight four additional units were studied for 48 hours with recordings made for 15 min every 45 min.

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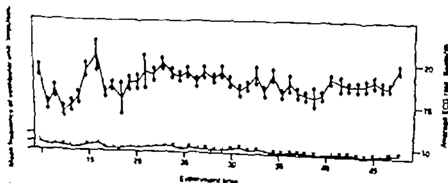


Fig. 6. ECG (ordinate on right) and statoreceptor firing rate (ordinate on left) during 48 hours of recording on the ground. The frog [illegible] kept at [illegible] water temperature of 1[illegible] °C. The unit responded throughout the experiment to just-above-threshold vibration of the water pump (for detail see text). Recording every 15 minutes in the hour. Mean and standard deviation both for ECG (black lozenges) and discharge frequency (empty triangles) ([illegible]000 impulses for each point).

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THE ACTIVITY OF THE VESTIBULAR STATORECEPTORS

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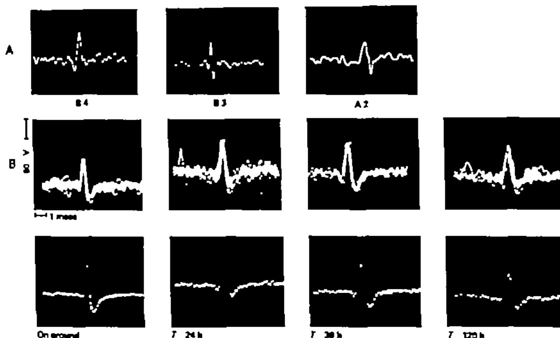


Fig 8 (A) Samples of impulses from units B4 B3 and A_. They are different in shape and duration and easily recognizable (B) Identification of B3 impulse data during the flight from *T* 9 h to *T* 120 h. Upper record Superposition of number of successive impulses Lower tracing Computerized erage of 60 impulses The telemetering ystem altered the spike shape slightly in comparison with the ground data. Owing to the lower frequency response of the telemetry ystem the spikes are flatter and longer in duration. The general parameters are however maintained naltered throughout the flight.

ficient of variation remained consistently 1±0 1 for all units Thus within the limits of this rather large variability the general characteristics of the basic activity at rest even in this preparation with all feedback systems intact (closed-loop) remained constant for several times the 24 hours cycle A constant trend toward decreased activity indicates however that the preparation cannot be considered to be absolutely physiologically normal The above statements are valid for a period starting no sooner than hours after the microelectrode implantation and for all the time in which the preparation is maintained in good condition (Gualtierotti & Alltucker 1966)

B In orbit (10^{-4} g max in all directions)

The OFO A experiment was conducted on two frogs (A and B) of approximately 0.350 kg weight with one microelectrode each implanted in the right and left vestibular nerves Accordingly the units were identified as A1 A_ B3 B3a, B4

Physiological condition

The condition of the preparations was continuously checked by inspection of the ECG Thus was particularly easy for Frog B as the ECG was clear from noise all the way through the experiment whereas for Frog A electric noise appeared after 24 hours of flight to such an extent that at *T*+48 the ECG was difficult to recognize It was felt therefore that the analysis of unit A2 should be limited to the first 40 hours of the flight as insufficient indication of the animal's condition laid the interpretation of the observed changes open to doubt. Unfortunately the records from unit A1 proved to be completely unsuitable for

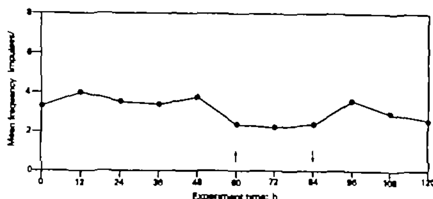


Fig 7 Ground control experiment Frog at constant *temperature 17°±0.5°C The activity at rest of a single* statoreceptor unit recorded for 120 hours, 30 minutes every 1 hours at the same time of the day Each dot corresponds to the average frequency of 000 spikes The *arrows indicate sudden spontaneous shift of the frequency* of discharge at rest by about 50%

test and trend evaluation) Directionally the receptors presented here were fairly homogeneous i e they responded to head down positions beyond an angle of 10° downward from the normal" plane In the bench position of the FOEP the animal s spatial orientation was normal" and no above threshold gravity component was included in the receptor field of these units In the orientation of the second batch of units studied after the flight one unit only showed changes in activity locked on to the minute vibration of the water pump as measured near the head (1–3 g 10^{-3} sinusoidal with a 20 msec period (Fig 6))

This unit was studied in order to compare its activity with unit B_3 that during the OFO A flight had become sensitive to a similar stimulus for a period of time (see later) All the tested frogs which were kept in good physiological condition showed an activity in the majority of fibres approached When it was difficult to find active fibres in the nerve during the microelectrode implantation procedure it was found that some deterioration of the preparation was in progress normally due to hypoxia in fact good oxygenation restored lively and constant activity throughout the nerve

Average rate of firing

All units studied showed a low rate of firing at rest with a range of between 1 and 4 impulses/sec The same pattern was recorded under water as in air The time history of the average rate of firing during several days did not show an increase in the general variability (Fig 7) It should be noticed that the environment was constant within very close limits The frogs were kept in perfect darkness throughout the experiment in a sound proof environment submerged in CO_2-free water at a temperature constant within 0 5°C with a steady PO_2 and hydrostatic pressure

Even under these conditions the definition at rest has to be clarified here it signifies that the proper input (acceleration) had a subthreshold value

The unit responding to the pump vibration (Fig 6) showed a rate of firing of the same order as that shown at rest (approximately 2 impulses/sec) The response to such a liminal stimulus consisted in the phase-locked synchronization with the vibration frequency (50 Hz)

This behaviour was constant throughout the entire 48 hours of recording during which the vibratory stimulus maintained the same parameters

Interval distribution and coefficient of variation

For each unit the interspike interval distribution (see Fig 4) as shown by the minimum interval and the mode remained closely unaltered during the entire experiment The coef

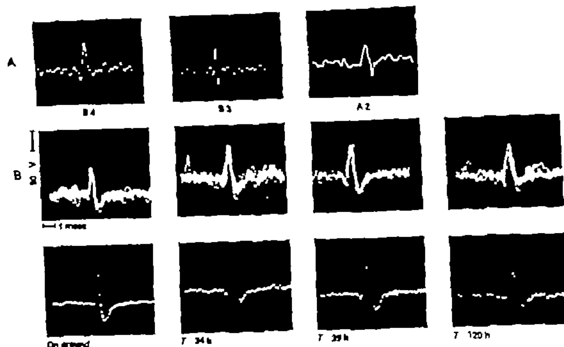


Fig. 8. (A) Samples of impulses from units B4, B3 and A2. They are different in shape and duration and easily recognizable. (B) Identification of B3 impulse data during the flight from *T* 9 h to *T* 120 h. Upper record: Superposition of number of successive impulses. Lower tracing: Computerized average of 60 impulses. The telemetering system altered the spike shape slightly in comparison with the ground data. Owing to the lower frequency response of the telemetry system the spikes are flatter and longer in duration. The general parameters are, however, maintained unaltered throughout the flight.

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B. In orbit (10 g max in all directions)

The OFO A experiment was conducted on two frogs (A and B) of approximately 0.350 kg weight with one microelectrode each implanted in the right and left vestibular nerves. Accordingly the units were identified as A1, A2, B3, B3a, B4.

Physiological condition

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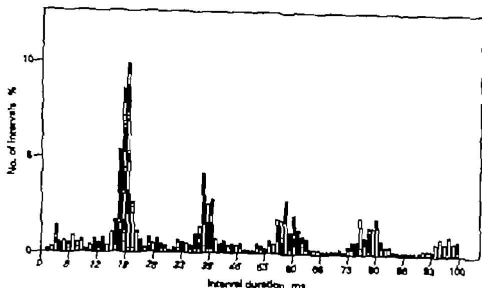


Fig 9 Interspike-interval histogram of unit B3 which during this period responded to the water pump vibration. The peaks shown in the figure correspond exactly to the 1 870 revolutions per minute of the pump

analysis Fig 8 shows that the units selected for analysis retained identical parameters throughout 120 h of observation Of the four units examined units A2 and B4 were at rest when not specifically stimulated by a centrifuge cycle Units B 3 and B 3 a showed a response to the vibration of the waterpump during some period of the flight The response to the pump vibration is demonstrated by typical peaks (20 msec apart) on the interspike histogram of the unit (Fig 9) The vibratory stimulus thus resulted in an effective input of sufficient strength to increase the average firing rate above the level recorded on the ground

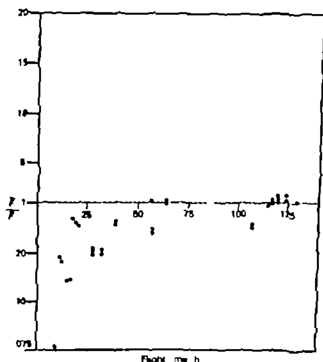


Fig 10 Unit B4 Change the ratio of the mean frequency during the flight (F) and the mean frequency at rest (F) during 130 h of orbital flight Note the change the rate of firing from a decrease of 1/15 to a peak increase of 20 times the mean frequency on the ground

All units showed in free fall a highly significant periodic change in activity of up to 20 times larger than the occasional fluctuations on the ground Fig 10 and 11 show such periodic fluctuations in activity for unit B 4 for up to 125 h and for unit A 2 for up to 40 h after injection into orbit Both units were free from external stimulation except when the centrifuge was activated When first observed the level of activity was considerably lower than that on the ground in both units The impulse activity is here expressed as the quotient of average activity in flight over average activity on the ground (F/F_0) The whole period of observation of unit A 2 falls within the period of reduced activity

In unit B 4 the initial period of reduced activity is followed by a large increase in the impulse discharge which lasts for approximately 50 h This is then followed by a second reduction in activity which in turn leads to a level of activity commensurate with that observed on the ground

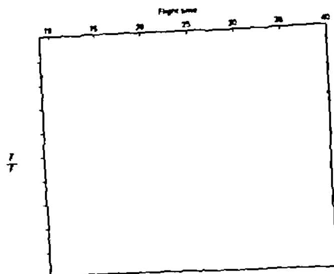


Fig. 11. Unit A 2 (same representation as in Fig. 10). During the flight the mean rate of firing at rest decreases progressively. F = mean frequency in orbit. F = mean frequency on the ground.

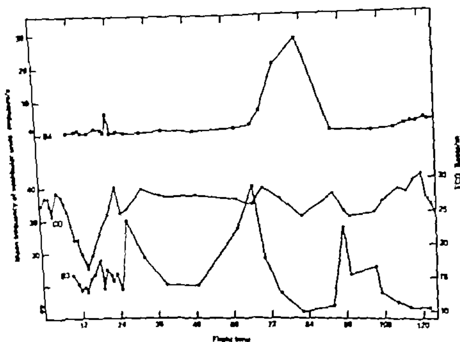


Fig. 12. Time history of the rate of firing during 125 h of orbital flight of units B 3 (lower record, round dots) and B 4 (upper record, square dots) and ECG of frog B (middle record, black triangles). On the left, outside the ordinate: mean frequencies on the ground (diamonds). All points represent the mean of 1000 impulses. Unit B 3 was stimulated by the vibration of the water pump; unit B 4 was not affected. Note the large decrease of the heart rate between T 9 h and T 4 h caused by a drop in the water temperature to 13°C due to faulty command to the thermoregulatory system. From T 4 h onwards the temperature control was working perfectly and the temperature was maintained between 16.5° 17°C.

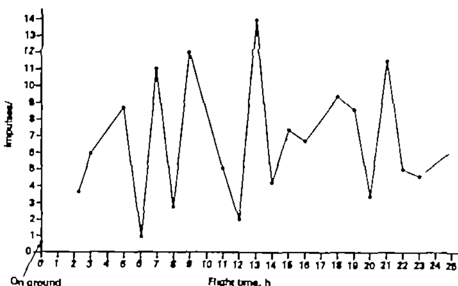


Fig 13 Changes of the intercycle frequency of firing during the first 25 h of the flight of unit B 3 a Periodical increase and decrease of frequency are shown up to nearly 10 times the activity level on the ground

Observation of numerous otolith-controlled units showed that the "basic" activity includes not infrequently bursts of a few closely spaced impulses representing intraburst frequencies up to 200 impulses/sec (Gualtierotti & Alltucker 1966) In orbit the incidence of such "bursts" increases to such an extent in unit B 4 that the whole of the "basic" activity may consist of frequent "bursts" alternating with periods of complete inactivity

Unit B 3 (also B 3 a (see page 20)) were sensitive to the vibration of the circulation pump (Fig 9) Their behaviour and that of unit 4 B is illustrated by Fig 12 and 13 for 120 h (B 4 and B 3) and 25 h (B 3 a) respectively It should be noted that the behaviour of unit B 3 a mirrors that of unit B 3 for the whole period of its evaluation As shown in Fig 12 there are large fluctuations in the activity of unit B 3 not only while it responds to pump vibration but also after approximately $T+80$ h when it ceases to do so For a few hours its level of activity now even drops below that recorded on the ground A scale factor accounts for the apparent absence of fluctuations in trace B 4 up to approximately $T+70$ h (compare however Fig 10)

Coefficient of Variation

The variation coefficients for units B 3 and B 4 of the same frog are very different The CV of B 3 is similar to the one typical of the units studied on the ground namely around 1 ± 0.1 while for B 4 owing to the frequent occurrence of "bursts" during the first 92 hours of flight the CV oscillated between 1 5 and 10 approx As soon as the "bursts" disappeared the CV returned to 1 (Fig 14) In unit A 2 and B 3 a the CV remained equal to 1 ± 0.1 throughout

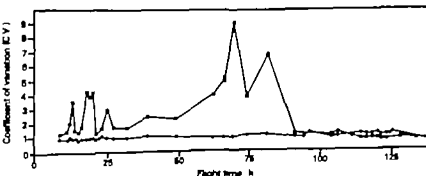


Fig 14 Coefficient of variation against time Unit B 3 (lower record round dots) and B 4 (upper record square dots) during 130 h of orbital flight

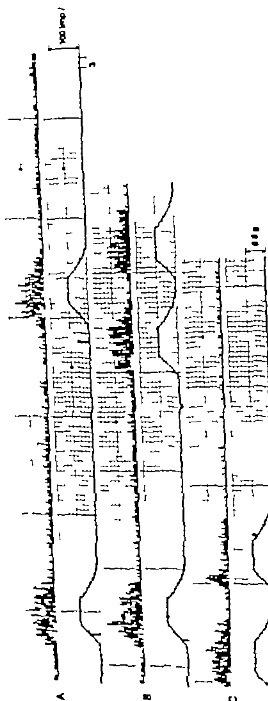


Fig. 15 Unit A on the ground F planation in the text

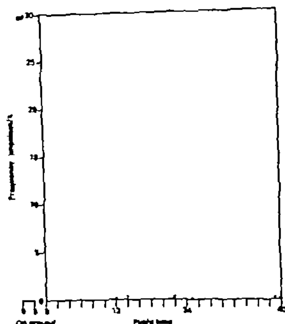


Fig. 16 Unit A orbit: Analysis of the activity at rest and during the second half of the centrifuge cycle at constant speed. The mean frequency of samples of approximately 700 impulses at rest and 25 impulses during stimulation is given by the round and square dot respectively. The analysis is limited to the first 40 h of the flight. frog A after this time did not show readable ECG and its physical condition could not therefore be fully assessed. This unit did not respond t the water pump vibration and is truly t zero stimulation between the centrifuge cycles. There is remarkable decrease in frequencies during the flight. The response to the spin cycles is also diminished. On the ordinate: Mean firing rate (impulses/sec). On the abscissa: Time in hours from lift-off. On the left of the ordinate, mean frequency at rest and response to the centrifuge cycles on the ground before the flight.

Responses to centrifuge spin cycles on the ground and in orbit

No data could be recorded during the first complete orbit (90 min) because of a temporary command failure which could fortunately be rectified from the second orbit onward. The responses of the various units to centrifuge spin cycles may now be described by selected examples taken from the case histories of the individual units.

Unit A2 yielding only 40 h of analysable flight record behaved on the ground as shown in Fig. 15. Trace A represents two slowly adapting tonic responses to centrifuge spin cy

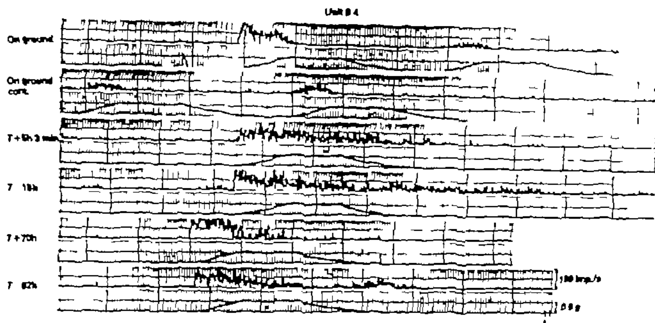


Fig 17 Unit B 4 on the ground and in orbit Description in the text.

cles at an interval of approximately two min showing similar characteristics Traces B and C (10 h later) Two widely spaced and three closely spaced stimuli result in practically unaltered response types with a certain progressive diminution in total impulse output when the stimuli follow closely upon another The behaviour of this unit during 40 hours of orbital flight is shown in Fig 16 In contrast to unit A 2 unit B 4 behaved on the ground like a pronouncedly phasic unit with fairly rapid adaptation during the constant velocity period of the spin cycle. Traces 1st and 2nd from top of Fig 17 illustrate this and the decline in gain on close repetition of stimulation Trace 3rd ($T+5$ h 3 m) shows that the unit s behaviour has changed from phasic to tonic with the characteristically slow adaptation Trace 4th ($T+15$ h) shows the unit s behaviour unchanged At $T+70$ h there is a return to faster

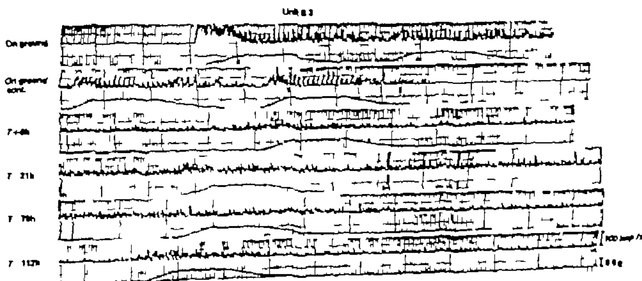


Fig 18 Unit B 3 on the ground and in orbit. Description in the text

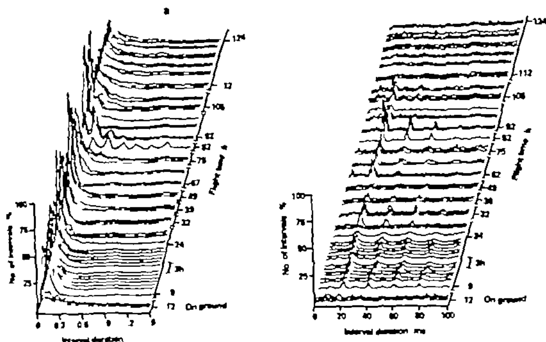


Fig. 19. Unit B3. Three-dimensional diagrams indicating the interspike interval distribution by means of interspike interval histograms displaying data on the ground followed by data throughout the orbital flight. In *b* the histograms are based on smaller classes (ms) and in *a* on larger ones (s). The peaks of the histograms in *b* correspond to the bursts of impulses following the peak vibration curves. Their average distribution is given in ... It is immediately evident that the alteration in the basic activity of this unit starts with the first record available at *T*+9 h of the mission and ends around 110 h. From 112 to 124 h the histograms are similar to the ones obtained on the ground.

adaptation and the response following upon deceleration of the centrifuge is followed by a short rebound of the discharge which is not untypical for responses in orbit.

As unit B4 was unaffected by pump vibration it presents us together with the relatively short lived unit A... with the most instructive picture of the behaviour of otolith-controlled vestibular units in "weightlessness". The records making up Fig. 17 do not show much of the long-term periodic fluctuation in basic resting activity and do not therefore clearly illustrate the effect of such fluctuations on response gain. This is largely due to the fact that the mean frequency of the "basic" activity is composed of high-frequency "bursts" and long inactive period.

Unit B3 having been for most of the orbital flight affected by pump vibration to which it responded by synchronized firing masking its basic resting activity, cannot be considered to have been truly deprived of stimulation when at rest in "weightlessness". On the ground it behaved like a slowly adapting tonic receptor.

It showed a pronounced response to the fluctuation in gravitational stimulation (1 Hz) due to the deviation of the centrifuge platform from the true horizontal. It also showed a decrease in gain of its response to closely spaced repetition of the stimulus (Fig. 18, traces 1st and 2nd from top). Trace 3rd (*T*+6h) shows a response to the spin cycle against the background of a fluctuating ongoing response to the pump noise. The gain of the slowly adapting response is relatively small with only a moderate phasic component. There appears to be an unexplained start of increased activity approximately 6 sec before the recorded start of the

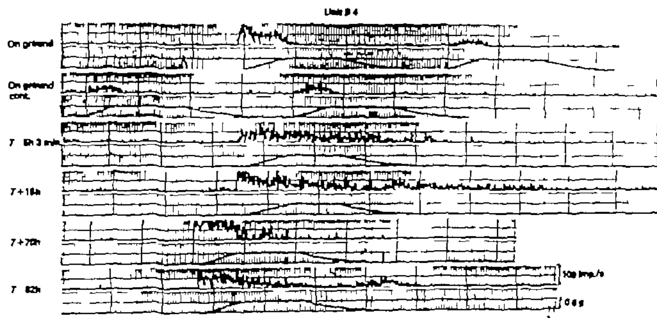


Fig 17 Unit B 4 on the ground and in orbit Description in the text.

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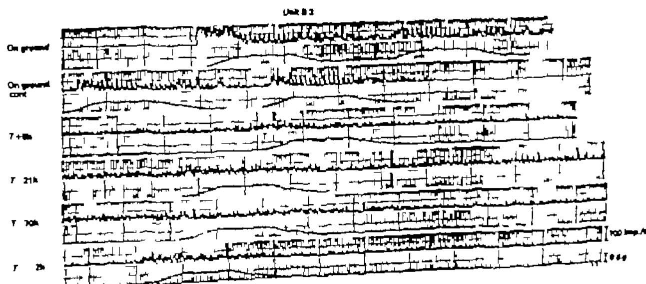
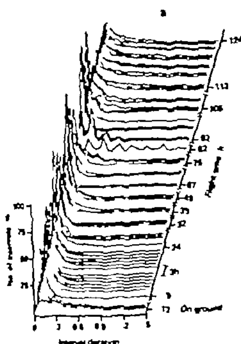


Fig 18 *Unit B 3* on the ground and in orbit Description in the text



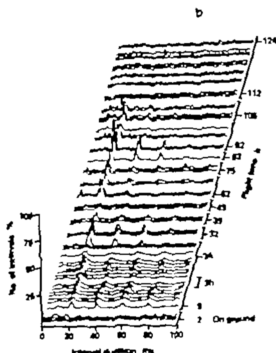


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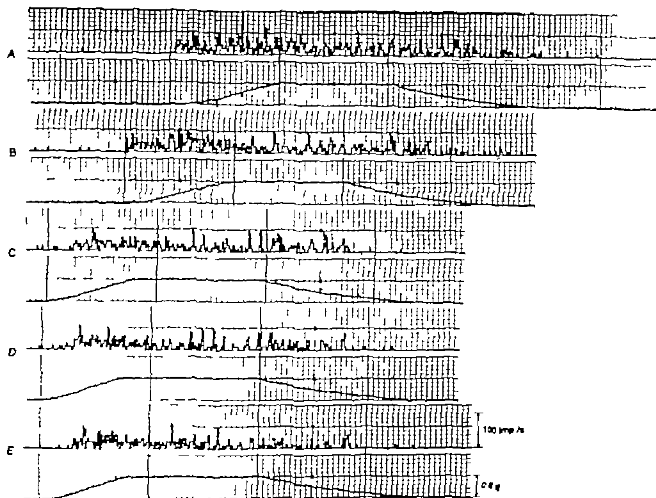


Fig 20 Unit B 3 a Responses on the ground (A and B) Two responses separated by a 20 minute interval followed by C D and E consecutive without a break The behaviour is similar to the one exhibited by unit B 3 v z a decrease in the amplitude and in the gain in responses to closely spaced spin cycles This non-adapting unit is a good example of a tonic receptor

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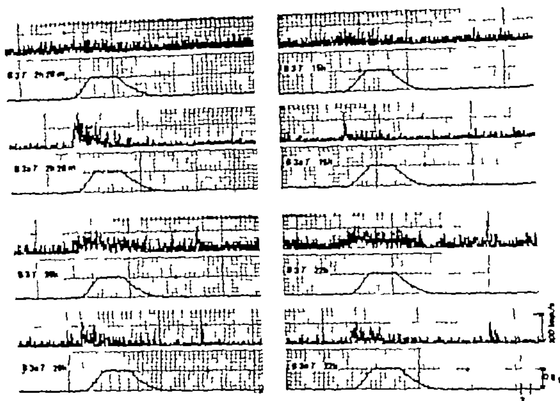


Fig. 21. Responses to the same centrifuge spin of two units (B3 and B3′) recorded from the same microelectrode during the orbital flight. Both units are tonic receptors and both did not respond to the water pump vibration on the ground but started responding to it in orbit. Note how both the intercycle activity and the responses to the centrifuge spin vary independently during the flight. In both units correlation seems to exist between the intercycle rate of firing and the amplitude of the response to the centrifuge spin cycle (see B3 T h 28 m compared with $T+20$ h and T 22 h, and unit B3′ at $T+2$ h 28 m compared with T 20 h). At T 15 h unit B3′ shows an evident change to phasic behaviour which is reversed at T 22 h.

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Discussion

METHODS

The experiments carried out both on the ground and in orbit were completely automatic, were planned in such a way as to last several days, were based on the recording of the action potentials of single units of the vestibular nerve of animals kept in good physiological condition and most of the environmental variables (temperature, PO_2, light, pressure etc.) were carefully controlled. A constant adequate stimulus could be applied periodically by a centrifuge according to a predetermined program that could be changed as a function of the results (preset stimulus).

The activity of the vestibular statoreceptors prepared for the flight was studied starting one day before launch and continuing during the orbital period for six days till the exhaustion of the power supply of the spacecraft. Thus seven days of recording became available derived from the same single

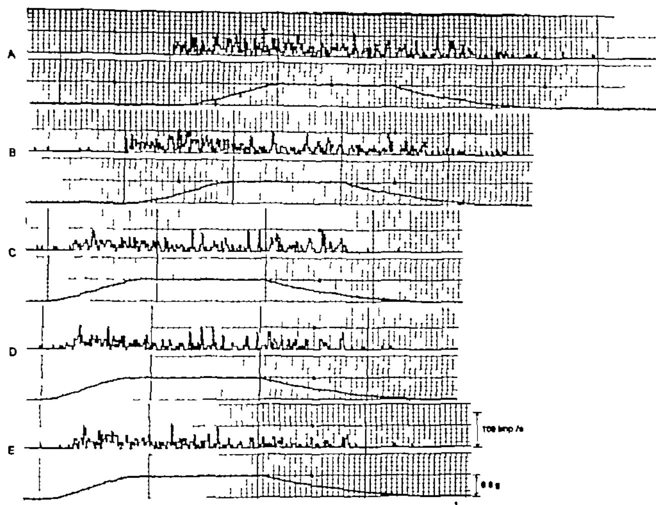


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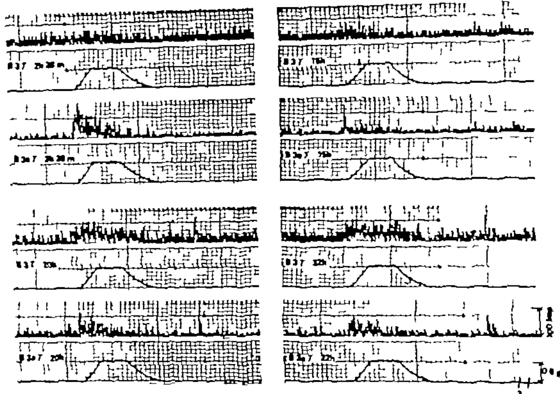


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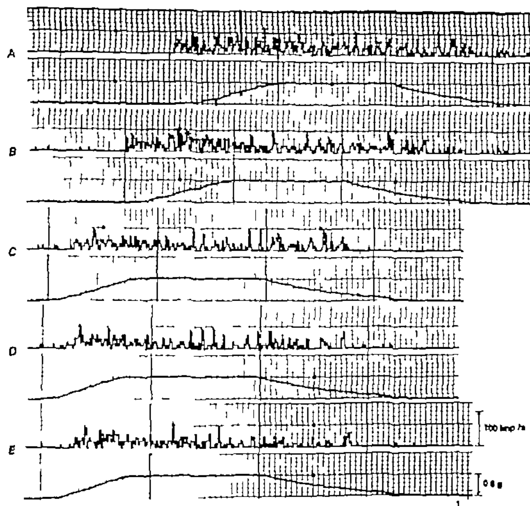


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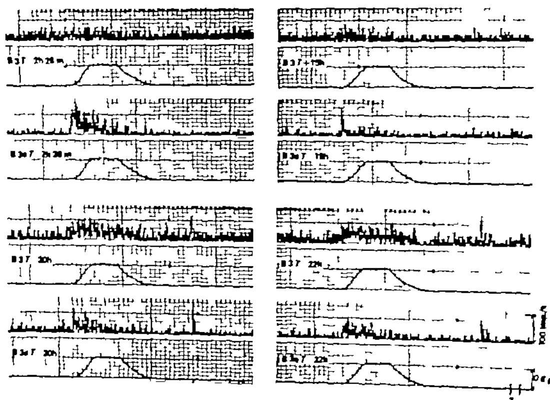


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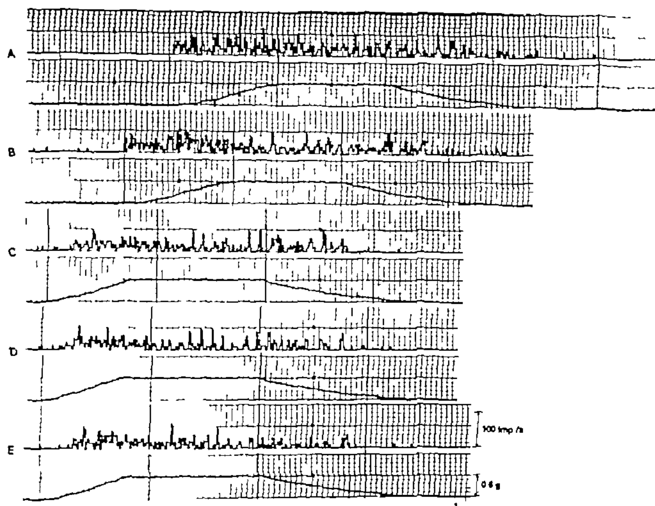


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reported so far in the literature are limited to relatively short-periods of acute experiments (Lowenstein & Roberts 1949 Rupert et al 1962 Kimm & Lischel 1971) There is no information on such activities observed for a sufficiently long time to analyse the general basic characteristics of the firing rate of the vestibular units for periods exceeding a possible daily cycle During the present experiments the impulse train data of the same single primary neurons of the vestibular statoreceptors have been recorded for the first time in a closed-loop system over a number of consecutive periods of 24 hours up to 6 in the carefully controlled environmental conditions provided by the FOEP

As a result the time history of the receptors activity could be studied as a function of the 24 hours span for a number of such cycles This would permit recognition of a possible rhythmical change

One may sum up the observations made on the four units in orbital flight as follows There is a significantly larger fluctuation of unit activity in the absence of the preset stimulus (centrifuge spin cycle) There is further a change in the gain of the response to the preset stimulus and to vibration. Thirdly there occur reversible changes in the mode of the response to the stimulus from tonic to phasic and vice versa. These observations appear to be exclusively associated with the condition of free fall because they have never to any significant extent been observed on the ground One may *therefore* ask *What is the chief effect of free* fall on the organ itself? There is no doubt that the *force* exerted by the otolith on the underlying otolith membrane or vice versa, the supporting force by the otolith membrane on the otolith organ is minimized by the absence of the gravitational acceleration vector The otolith mass however can be assumed *to be* unaltered at least during the period of the present run of observations *In the* earth-gravitational field on the ground one *may imagine* the otolith membrane *to be tensioned by* the weight of the otolith supported by the suspension structures of the macula within the vestibulum. This may be assumed to result in a structural stiffening of the macula harbouring the orderly arrangement of the population of hair-cell receptors. It would be surprising if the mechanical properties of the macula were therefore not affected by the "unloading" of the macula in free flight It may be assumed that the macula so unloaded becomes a "play ball" of any random forces impinging upon it in orbit, apart from the fact that its response to mechanical deformation is very likely to be modified not only so far as the whole macula is concerned but especially perhaps regionally with the strong possibility of configurational changes fluctuating in time

It may now be useful to investigate the chief observations of unit behaviour in orbit in the light of these supposed changes in macula configuration

The fact that the first two hours and twenty-eight minutes of recording from the units in orbit were lost owing to transmission failure prevents us from knowing whether the immediate effect of the establishment of the free-fall condition was a lowering or a rise in unit activity *The now generally accepted* hypothesis *in* the interpretation of the mode of *functioning* of vestibular hair-cell receptors is *that* they respond chiefly if not exclusively to shearing forces tangential to the plane *of the* epithelium in which they are lodged *This hypothesis replaced earlier hypotheses operating* with the possible mechanism of changes in pressure or tension exerted on the hair processes of the receptor cell Recently *it was pointed out* however that changes *in* otolith pressure could be translated into changes *in* shearing force at the base of the hair processes *and thus be responsible for changes in unit* activity (Benson & Barnes, 1973) *If this be* so we would have to consider the possibility *in the* case of the present *experiments* that the unloading of the otolith membrane *may result* in significant changes in the spatial disposition *in the hair processes* in a shearing direction and may *therefore* be responsible for changes

vestibular units The absence of significant alterations in the action potential parameters appears to indicate that the basic impulse generating mechanism was unaffected by the free fall condition

These results seem to prove that the microelectrode technique in every way satisfied the requirements

The FOEP proved to be a perfect solution for maintaining physiological conditions in an animal under water It will provide a suitable tool for new experiments both in space and in the laboratory performed on fish or amphibians aquatic animals in which the environmental conditions are more easily controlled and monitored than in terrestrial ones However some inconveniences existed The water circulation system for instance introduced an unwanted artifact in the form of water pump vibration

WELFARE UNDER WATER

A frog can survive under water for several weeks provided the temperature is not raised above 14–15°C at a normal atmospheric PO_2 namely 155 mm of mercury (Serfaty & Gueut al 1943) In these conditions however the O_2 consumption is reduced to 70% of the normal value in air and survival is achieved only by the corresponding decrease of the metabolic rate (Leivestad 1960) This cannot therefore be considered completely satisfactory for normal metabolism The O_2 transport through the skin is due to passive diffusion only and therefore is bound to be proportional to the PO_2 of the environment (Krogh 1904 Dolk & Postma 1926) The thickness of the skin is such that a sizeable O gradient must exist between the environmental PO_2 and PO_2 of the blood in the capillary network Both in the air and in respiration under water most of the CO_2 if not all is eliminated through the skin whereas the O_2 in air respiration is absorbed partly from the skin at a constant level throughout the year and partly through the lungs with seasonal variation. (Jullien et al 1958 Bastert 1929)

It is obvious that the efficiency of the skin respiration depends on the surface/mass ratio of the animal the amount of O_2 provided being proportional to the surface and the amount of O_2 consumed during the metabolic activity to the mass. In the large bull frog the ratio is not particularly favourable As most of the O_2 is consumed by the muscles during exercise a partially paralyzed frog would need less O_2 than a fully active one

From what is stated above it can be concluded that the animal under water can survive only within rather narrow limits of temperature On the high side the frog incurs progressive asphyxia on the cold side the frog can stand even below freezing-point temperatures, but at 4–8°C the firing of the nerve fibre practically ceases

RESULTS

A gravity sensitive receptor or tonic statoreceptor is identified in the earth gravitational field by responding to a steady position of the head (or a steady linear acceleration) with a stationary mean firing rate after a more or less pronounced adaptation (Gualtierotti & Gerathewohl 1965 Vidal et al 1971) In the case of the present investigations no attempt was made to identify the origin of the activity recorded with respect to a specific otolith organ since in an orbital experiment post mortem examination is precluded by the fact that the preparation cannot be recovered However in this series of experiments units were selected whose highest sensitivity was to tilt in the sagittal plane This indirectly suggests that these units may have been controlled by the utriculus Any such localization must however remain extremely tentative since parts of the sacculus macula lie in a plane compatible with the responses

All data on the vestibular statoreceptor activity both at rest and during stimulation

far in the literature are limited to ort-periods of acute experiments (& Roberts 1949 Rupert et al & Luschei 1971) There is no in- n such activities observed for a long time to analyse the general cteristics of the firing rate of the nits for periods exceeding a possi- ycle During the present experi- npulse-train data of the same single urons of the vestibular stato- ive been recorded for the first time l-loop system over a number of : periods of 24 hours up to 6 in the ntrolled environmental conditions r the FOEP

it the time history of the receptors ıld be studied as a function of the 24 for a number of such cycles This nt recognition of a possible rhyth- ge

' sum up the observations made on its in orbital flight as follows. There ficantly larger fluctuation of unit the absence of the preset stimulus spin cycle) There is further a the gain of the response to the preset nd to vibration. Thirdly there occur changes in the mode of the response nulus from tonic to phasic and vice ese observations appear to be ex ssociated with the condition of free se they have never to any significant n observed on the ground. One may ask. What is the chief effect of free : organ itself? There is no doubt that exerted by the otolith on the under lith membrane or vice versa the g force by the otolith membrane on h organ is minimized by the absence avitational acceleration vector The ass, however can be assumed to be l at least during the period of the run of observations. In the earth- onal field on the ground one may im- : otolith membrane to be tensioned by ht of the otol th supported by the suspension structures of the macula within the vestibulum This may be assumed to result in a structural stiffening of the macula harbouring the orderly arrangement of the population of hair-cell receptors It would be surprising if the mechanical properties of the macula were therefore not affected by the "unloading" of the macula in free flight. It may be assumed that the macula so unloaded becomes a play ball" of any random forces impinging upon it in orbit, apart from the fact that its re sponse to mechanical deformation is very likely to be modified not only so far as the whole macula is concerned but especially perhaps regionally with the strong possibility of configurational changes fluctuating in time

It may now be useful to investigate the chief observations of unit behaviour in orbit in the light of these supposed changes in macula con figuration.

The fact that the first two hours and twenty-eight minutes of recording from the units in orbit were lost owing to transmis- sion failure prevents us from knowing whether the immediate effect of the establishment of the free-fall condition was a lowering or a rise in unit activity The now generally accepted hypothesis in the interpretation of the mode of functioning of vestibular hair-cell receptors is that they respond chiefly if not exclusively to shearing forces tangential to the plane of the epithelium in which they are lodged This hypothesis replaced earlier hypotheses operat ing with the possible mechanism of changes in pressure or tension exerted on the hair proces- ses of the receptor cell Recently it was pointed out however that changes in otolith pressure could be translated into changes in shearing force at the base of the hair processes and thus be responsible for changes in unit activity (Benson & Barnes 1973) If this be so we would have to consider the possibility in the case of the present experiments that the unloading of the otolith membrane may result in significant changes in the spatial disposition in the hair processes in a shearing direction and may therefore be responsible for changes

vestibular units The absence of significant alterations in the action potential parameters appears to indicate that the basic impulse generating mechanism was unaffected by the free fall condition

These results seem to prove that the microelectrode technique in every way satisfied the requirements

The FOEP proved to be a perfect solution for maintaining physiological conditions in an animal under water It will provide a suitable tool for new experiments both in space and in the laboratory performed on fish or amphibians aquatic animals in which the environmental conditions are more easily controlled and monitored than in terrestrial ones However some inconveniences existed The water circulation system for instance introduced an unwanted artifact in the form of water pump vibration

WELFARE UNDER WATER

A frog can survive under water for several weeks provided the temperature is not raised above 14–15°C at a normal atmospheric PO_2 namely 155 mm of mercury (Serfaty & Gueutal 1943) In these conditions however the O_2 consumption is reduced to 20% of the normal value in air and survival is achieved only by the corresponding decrease of the metabolic rate (Leivestad 1960) This cannot therefore be considered completely satisfactory for normal metabolism The O_2 transport through the skin is due to passive diffusion only and therefore is bound to be proportional to the PO_2 of the environment (Krogh 1904 Dolk & Postma 1926) The thickness of the skin is such that a sizeable O_2 gradient must exist between the environmental PO_2 and PO_2 of the blood in the capillary network Both in the air and in respiration under water most of the CO_2 if not all is eliminated through the skin whereas the O_2 in air respiration is absorbed partly from the skin at a constant level throughout the year and partly through the lungs with seasonal variation (Jullien et al 1958 Bastert 1929)

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tween these two types of response is now generally interpreted as a difference in the degree and speed of peripheral adaptation. There is at present no mental model available that could link the observed changes in orbit to any possible adaptive process in the sensory cell and its first-order neuron especially as such processes themselves are far from being understood

To sum up it appears reasonable for the present to confine oneself to the consideration of the mechanical circumstances and their possible influence on unit activity as discussed above

The question arises what if any relation the observed effects of "weightlessness" on the behaviour of single otolith-controlled vestibular units have on the orientation and wellbeing of the astronaut in orbit Although our primary concern are problems of vestibular physiology as such it appears desirable to ask whether our data can suggest possible causes of space sickness or orientational maladjustment It is obvious that an analysis of clinical syndromes would have to be based on rigorously designed and executed tests carried out on space personnel in an orbiting spacecraft, but we believe that the mismatch of information that could possibly be associated with the modification in response behaviour of the otolith-controlled units observed in this experiment as against the background of other non-gravitational sources of information could be expected to contribute in a specific manner to such syndromes

It could be argued that the number of units observed in orbit is too small to permit the drawing of significant conclusions about the organ's response to "weightlessness" Against this must be set the fact that the results reported here rest on seventy recordings per individual unit (twenty on the ground and fifty in orbit) carried out over a period of approx 180 hours (24 on the ground and 155 in orbit) We are therefore dealing with a situation in which individually identifiable units furnish us with controlled observations in an extended time dimension This is, in fact the first time that individual first-order vestibular units have been observed continuously for such prolonged periods of time in a chronic preparation of a physiologically near intact animal

Summary

The otolith-controlled activity at rest or under the influence of low-intensity vibratory stimulation and the responses to pre-programmed centrifuge spin cycles of single 1st-order axons of the vestibular nerve of the bull frog has been recorded for up to 7 days through extracellular microelectrodes in the 1 g earth gravitational field and in an orbital satellite (10^{-} – 10^{-} g max)

During the recording period 2 bull frogs, intact but for the partial paralysis of the 4 limbs, were kept under standard environmental conditions (PO_2 temperature illumination, pressure acceleration) in a specially built experimental container completely filled with water in which the animals were submerged for the duration of the experiment The environmental variables indicated above and the ECGs were monitored continuously

The activity at rest in the 1 g gravitational field was irregular The coefficient of variation for the statoreceptor activity was found to be close to 1

In orbit a significantly larger fluctuation of the units activity in the absence of the preset stimulus (centrifuge cycle) was observed as well as a change of gain of the responses to the preset stimulus and to vibrations. One of the most striking effects of "weightlessness however was a reversible change in the mode of response to the preset stimulus from tonic to phasic and vice versa.

in the overall unit activity Changes in otolith pressure need not be expected to be uniform over the whole otolith membrane but could have a patchy distribution owing to the lack of stiffening caused by unloading and this may account for the lack in uniformity in unit behaviour in orbit

So far as the fluctuations in gain are concerned it appears to us that configurational changes in the membrane supporting a given unit may influence its gain by either increasing or decreasing the efficiency of the mechanical deformation by the stimulus (mechanical gain) Nothing worth while can be said at present about any possible influence of weightlessness on the gain of the mechanoelectric transduction process This would involve synaptic and membrane-based processes in a way impossible to assess

It may be argued that the changes observed in free fall could be due to extravestibular influences first and foremost among these effects that reach the units via the efferent system innervating the hair-cell Although the functional role of the vestibular efferent system has not as yet been conclusively established in any organism there are certain assumptions which would be compatible with a fluctuation in unit activity in response either to its own activity level at any given moment or with that in extra vestibular systems such as stretch and joint receptors in neck and limbs integumental visceral and vascular receptors a s o

In the case of the present experiments we can to a large extent exclude the responsibility of visceral and vascular sources for changes in efference because the animal is completely immersed in water Moreover the nerve supply to the limbs was almost completely interrupted only a small proportion of the afference from the hind legs remaining intact The chief source of extra vestibular afference would therefore be confined to the head neck and intervertebral joints However the differential density of bone and soft tissues is without possible influence in free fall Any change in the inflow of efference into the vestibular organ could therefore only be random and such randomness might itself be a mediate consequence of receptor instability contributing to its total extent

In this connection it may be called for to deal with one possible criticism of our experimental procedure It may be asked why a control experiment was not performed in this mission based on the interruption of the efferent pathway either in one of the two frogs or in the second labyrinth of one of them In answer to this it must be categorically stated that the exclusion of the efference by proximally sectioning the eighth nerve or by central nervous lesions was out of the question because any interference with the blood circulation would nullify the value of the experiment not only by jeopardizing the prolonged survival of the animal but equally important by impairing the physiological condition of the end organ possibly also by initiating degenerative changes in the peripheral system during the period of the orbital experiment

The only possible way of interfering with the efference in a less traumatic manner would be the administration of a drug known to block the efferent synapse without affecting the afferent one This has recently moved into the realm of possibilities Not only has it become fairly certain that the afferent and efferent synapses conduct by means of different transmitter substances (Iurato et al 1971) but Flock & Russell (1973) have claimed to have succeeded in pharmacologically blocking the efferent synapse in the lateral line organ of the burbot (Lota lota) without affecting the basic transmission process in the afferent synapse apart from producing its disinhibition Such possibilities were not available at the time of the OFO A experiment here described but may open promising possibilities for any future experiment of this kind

One of the most striking effects observed in free fall was the reversible change from a tonic to a phasic mode of response to the centrifuge spin cycle and vice versa The difference be

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The results are discussed in the light of the likely mechanical changes caused by the unloading of the macula in free fall and of possible modifications in the efferent control mechanism and in adaptive processes

Zusammenfassung

Die Aktionspotentiale einzelner Neurone I Ordnung des Otolithensystems von Ochsenfröschen wurden mit extrazellulären Mikroelektroden im Gravitationsfeld der Erde (1 g) und in einem Satelliten in einer Erdumlaufbahn (10^{-4}–10^{-3} g max) abgeleitet. Zusätzlich wurden vorprogrammierte vestibuläre Reize nämlich niederfrequente Vibration und centrifugale Beschleunigung angewandt

Die zwei Ochsenfrösche wurden durch Nervendurchtrennung an den vier Extremitäten immobilisiert Die Umweltbedingungen (PO_2 Temperatur Beleuchtung Druck Beschleunigung) wurden durch Verwendung eines speziellen life support system in welchem die Tiere unter Wasser für die gesamte Dauer des Experimentes untergebracht werden möglichst konstant gehalten Die Aktionspotentiale im 8 Hirnnerven und das EKG wurden kontinuierlich registriert

Das Entladungsmuster im 1 g Schwerefeld war auffallend unregelmäßig Der Variationskoeffizient für die Statoreceptoren Aktivität lag im Bereich von 1

Im schwerelosen Orbitalflug war die Fluktuation des unitären Entladungsmusters schon im ungereizten Zustand signifikant größer als auf der Erde Außerdem wurde eine Änderung der Empfindlichkeit der Einheiten gegenüber dem vorgegebenen Beschleunigungsreiz und gegenüber Vibration festgestellt Der überraschendste Effekt der Schwerelosigkeit war aber die reversible Änderung in der Reaktion der Einheiten gegenüber einem vorgegebenen Reiz zwischen einer tonischen zu einer phasischen Reaktionsform und umgekehrt

Die Ergebnisse werden diskutiert hinsichtlich wahrscheinlicher mechanischer Änderungen die durch Entlastung der Macula im freien Fall eintreten und außerdem hinsichtlich möglicher Änderungen in der efferenten Kontrolle der Macula und im Hinblick auf adaptive Prozesse

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SUPPLEMENT 335

Experimental Aural Barotrauma

Electrophysiological and Morphological Findings

BY

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From the Department of Otolaryngology University of Washington, Seattle, Washington 98195, USA

Introduction

INCIDENCE

Aural barotrauma is a significant problem in otolaryngology. New cases of temporary and permanent hearing loss from barotrauma continue to be reported (1, 2, 3, 4, 5, 6, 7, 8). With more and more people engaged in recreational diving activities the number of cases is increasing. It has been estimated that five million people in the United States are utilizing SCUBA diving equipment (9). As early as 1944 a Naval study reported the incidence of aural barotrauma to be present in 5 to 20 per cent of all diving and flight operations (10). Aural barotrauma is not only encountered at high altitudes, great depths of water and long exposures to increased pressure, but can occur with recreational diving at shallow depths after short periods of time. Symptoms of aural barotrauma are usually seen in the first six to ten feet and are greatest at eleven to twenty feet of descent (9). It has been reported that most tympanic membranes will rupture at one-half atmosphere of pressure differential across the drum (1 atmosphere = 33 feet) (11).

DEFINITIONS

Aural barotrauma is the damage to the ear resulting from a difference between middle ear pressure and environmental pressure (12). Throughout the literature there is a broad mixture of terms relating to this entity, e.g., alternobaric trauma, hyperbaria, barotitis media, barotitis, inner ear barotrauma, otitic barotrauma, otic barotrauma, aero-otitis, salpingo-tympanitis, aviator's ear, caisson worker's deafness, caisson disease.

Often confused clinically with and sometimes indistinguishable from aural barotrauma in the otolaryngology literature is a different entity called decompression sickness ("bends"). This is ear pathology resulting from total body release of nitrogen bubbles into the cochlea's intravascular endolymphatic or perilymphatic system, causing mechanical damage and tissue anoxia. The fact that this pathology is confused in the clinical and experimental literature is unfortunate and inappropriate. The etiology and pathology associated with aural barotrauma and decompression sickness indicate that these conditions should be viewed as separate entities. Moreover, an analysis of the mechanisms underlying aural barotrauma requires that we strictly define the associated changes with careful consideration for site and type of pathology. The literature on barotrauma may be examined under the broad categories of *middle ear barotrauma* and *inner ear barotrauma*. Experimental investigations on animals provide the means by which mechanisms underlying this pathology may be evaluated.

MIDDLE EAR BAROTRAUMA

Middle ear barotrauma is the most common medical disorder experienced by divers (12). It generally can be graded as to severity on otoscopic examination. The associated middle ear changes are time related (13) yet some can occur in the first five minutes (14). There is general agreement in previous reports on the stages of damage noted with increased pressure exposure (8, 12, 13, 14, 15, 16). They are as follows:

1. Retraction of the tympanic membrane.
2. Dilation of tympanic membrane blood vessels around the malleus and in pars flaccida.
3. Edema of the mucous membranes lining the middle ear space.

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pressure conditions. Flisberg et al. (22, 23) applied negative pressure to the mastoid air cell system of human patients and observed a direct relationship of increasing pressure to the amount of clear fluid transudate present. Mc Cormick et al. (24) is the only available report which relates electrophysiological with mor phological changes seen with experimental barotrauma. However in this study it is not possible to separate the effects of barotrauma from concomitant effects of decompression sickness.

PURPOSE

The purpose of the present investigation was to simulate aural barotrauma in an experimental animal model by introducing various longstanding pressures directly into the middle ear space of the guinea pig. Thereby electrophysiological responses of the cochlea and histopathological middle and inner ear changes could be examined, graded and an attempt made to relate them to each other

Material and Methods

Thirty-eight young healthy random strain guinea pigs weighing 250 to 400 grams were used. All animals demonstrated a Preyer's reflex and a normal middle ear at the time of surgery Electrophysiological data is based upon observations in thirty-five animals. Thirty animals were subjected to histopathological studies. The guinea pigs were divided into two experimental groups Group I consisted of twenty animals subjected to a continuous sustained specified pressure for a 120-minute period. Group II consisted of eleven animals. They were also subjected to 120 minutes of sustained pressure except that the pressure was returned to zero every twenty minutes for brief electrophysiological readings and then promptly restored to the specified sustained pressure. Four animals were used as controls

Animals were anesthetized with Methoxyflurane inhalation anesthesia, underwent a tracheostomy and were artificially respirated with a Palmer small animal respirator (25). Body temperature was monitored by a rectal probe and maintained at 36 C through a feedback system coupled to a heating pad beneath the animal. An electronic heart monitor was in operation throughout each experiment to help assure the animal's physiological stability The animal was placed in a head holder with an occipital screw and an anterior jaw clamp these held the animal's head securely for experimental manipulation.

After a surgical plane of anesthesia was established and the animal determined to be physiologically stable the bulla was exposed. The middle ear space was exposed by drilling a small hole in the bulla. The hole was widened until the round window was visualized and any small bone fragments that entered the middle ear space were removed. A platinum alloy ball electrode (0.007-inch diameter) coated with Insul-X was carefully placed on the round window membrane with the aid of a micromanipulator and cemented in position at the opening in the bulla with dental acrylic. A 23-gauge cannula with the tip just within the bulla was cemented in place adjacent to the electrode. Via this cannula middle ear pressure was varied directly For animals in one group (Group II), a small inspection hole was left in the dental cement and occluded with clay during pressure exertion. This small inspection hole permitted visualization of the middle ear space and removal of fluid at the end of the experiment. In Group I, the bulla was closed completely with the dental cement.

All experiments were performed in a double-walled soundproof chamber with all anesthetic, sound-generating and recording equipment out side Sound stimuli were presented to the animal

Table I *Suggested etiologies to sensorineural hearing loss caused by aural barotrauma*[a]

I Pressure influences on round and/or oval window by way of Eustachian tube and/or tympanic membrane
Round window membrane rupture Goodhill[a] (1971) Edmonds & Thomas (1972) Pullen[a] (1972) Goodhill et al (1973) Freeman et al. (19 4)
Perilymphatic oval window fistula Goodhill[a] (1971) Goodhill et al (1973)
Action on oval window-sheering forces on cochlea Cooke (1966) Eichel & Landes (1970)
Valsalva—forced stapes movements—cochlear stress lesions Macfie (1964) Edmonds & Thomas (1972) Freeman & Edmonds (1972)

II Pressure influences on cochlea from CSF
Increased venous sinus pressure Simmons (1968)
Increased CSF-pressure Goodhill (1971)

III. Vascular and blood disorders in the cochlea.
Hemorrhagia Heller et al. (1900) Hill[a] (191) Vail (1929) McCormick et al. (1973)
"*Bubble*" *formation, gas release* Wilson (1972) Compere (1974)
oxygen Wagemann (1962) Kessler (1969)
nitrogen Compere (1974)
Hypercoagulation, emboli trombus, erythrocyte aggregation Heimbecker et al. (1968) Philp et al. (1971) McCormick et al (1973)

IV Gas release in cochlear lympha
Decompression sickness Boot (1913) Vail (1929)

V Influences on middle ear dynamics
Teed (1944) Haines & Harris (1946)

VI Other
Labyrinthitis, neuritis Boot (1913)
Functional neuro-vascular angioneurotic mechanism Borasi & Sperati (1967)
Vasomotor dysfunction Kessler (1969)

[a] Visually or histopathologically confirmed.

4 Transudation of serous fluid into the middle ear space

5 Rupture of blood vessels in the tympanic membrane and middle ear resulting in hemorrhage in the middle ear space

6 Rupture of the tympanic membrane with or without displacement of the ossicular chain.

Haines (16) performed audiometry on over 6 000 men before and after 50 lbs./sq in experimental test dives. He found little effect on hearing except when the middle ear contained serosanguinous fluid

INNER EAR BAROTRAUMA

While the interest in hearing impairment in divers has focused on the middle ear it was recently emphasized that inner ear hearing loss may also result from aural barotrauma. Inner ear barotrauma may also occur simultaneously with middle ear barotrauma often with spontaneous recovery (13) However Freeman and Edmonds (4) reported five patients with persistent sensorineural deafness of which only one had middle ear hemorrhage There are now numerous reports of permanent hearing loss from diving The exact etiology of these cases is often obscure due to the lack of confirmed pathology and also because of a lack of pre incident audiograms (4) Table I shows a compilation of suggested etiologies of inner ear barotrauma A few clinically and experimentally supported etiologies are included As can be seen, the only cases supported by clinical evidence include round window membrane rupture or an oval window fistula whereas, the experimental evidence indicates inner ear hemorrhages or blood component abnormalities of etiologic significance for inner ear barotrauma.

EXPERIMENTAL INVESTIGATIONS

Presently there is little experimental data published aiming at substantiating the many suggested theories of aural barotrauma. Some electrophysiological work has been done in cats and guinea pigs on the effects of static pressure on middle ear dynamics (17 18 19 20). These investigations show a correlation between increased negative and positive pressure, decreased output function and increased middle ear impedance. Miller (21) subjected cats with an open bulla to hyperbaric conditions in a diving chamber A subsequent loss of 15 to 20 dB was noted in the cochlear microphonic (CM) response while the animals were pressurized. Since the bulla was opened, however no differential pressure existed across the tympanic membrane and thus the experimental model did not duplicate the usual barotraumatic

pressure. For Group II animals the final measures were also taken after fluid buildup was removed from the middle ear space. Suction applied via a cotton wick to the round window area was used to remove any fluid.

Three animals in the study were excluded from the final electrophysiological results because of technical preparation errors. However these animals were evaluated morphologically.

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Results

ELECTROPHYSIOLOGICAL OBSERVATIONS

Effects on the one microvolt CM input–output functions and N_1

The basic cochlear electrophysiological results obtained from this study are illustrated in Fig. 2 through 5. Fig. 2 shows changes in the one microvolt CM contour at zero pressure after various negative pressures were applied for 120 minutes. The pressures range from −50 to −700 mm H_2O as noted. In general, except for the lowest frequencies examined, the response is reasonably flat across frequencies with an approximate 10 dB difference separating the animals run at −50 and −100 mm H_2O from the animals run at −200 to −400 mm H_2O. There is a difference in sensitivity of approximately 20 dB separating the −200 to −400 mm H_2O group from the −500 to −700 mm H_2O

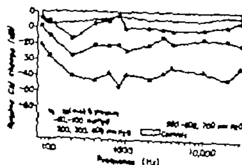


Fig. 2. Mean 1 μV CM difference scores at 0 pressure after 120 minutes with sustained negative pressure (Group I animals).

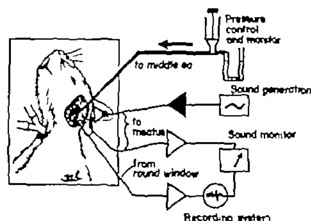


Fig 1 Diagram of experimental design for present electrophysiological experiments.

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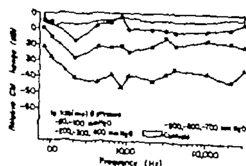


Fig. – Mean 1 μV CM difference scores at 0 pressure after 120 minutes with sustained negative pressure (Group I animals).

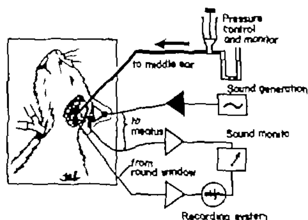


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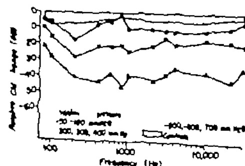


Fig. 2. Mean 1 µV CM difference scores at 0 pressure after 120 minutes with sustained negative pressure (Group I animals).

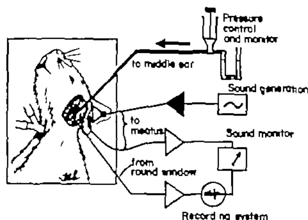


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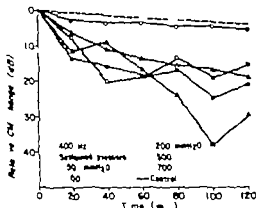


Fig. 6. Time course changes in the 1 μV CM for individual animals (Group I) subjected to 120 minutes of sustained negative pressure.

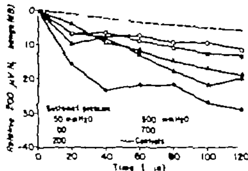


Fig. 8. Time course changes in the 200 μV N_1 for individual animals (Group I) subjected to 120 minutes of sustained negative pressure.

tive pressure, a graduated decrease in cochlear output occurs and appears as a parallel shift in sensitivity. Similar observations were made in other animals at different negative pressures.

Development of electrophysiological effects

Figs. 6 through 9 show the time course development of the electrophysiological results presented in Figs. 2 through 4. In Fig. 6, the change in the one microvolt CM at 400 Hz with various negative pressures ranging from −50 to −700 mm H_2O over a two hour period is demonstrated. In general, there is a graduated progressive loss in sensitivity with time. This same basic change was noted in other frequencies tested, but the response at 4 000 Hz was more variable.

Fig. 7 demonstrates the change in the one microvolt CM at 400 Hz with time for positive pressure animals ranging from +400 to +600 mm H_2O. Except for the animal run at +600 mm H_2O, there was no change in response. This latter animal had a perforated tympanic membrane by the end of the experiment. From the data in this figure it is tempting to suggest that this perforation occurred between 20 and 40 minutes following pressure onset. However the absence of any major effect of perforation alone (black triangle) makes this suggestion difficult.

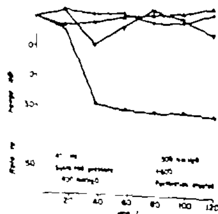


Fig. 7. Time course changes in the 1 μV CM for individual animals (Group I) subjected to 120 minutes of sustained positive pressure.

Time course development for N_1 data is demonstrated in Figure 8. As with the CM data (in Fig. 6) there also is a decrease in sensitivity with time and increasing pressure. Animals run at other negative pressures (not shown in Fig. 8) fit in an orderly sequential manner based on their respective pressures.

The time course development of the CM and N_1 effects is not due to applied pressure alone. This is demonstrated in Fig. 9. This figure summarizes the mean changes in the one microvolt CM at zero pressure readings over time in seven animals from Group II. This data demonstrates a graduated decrease in sensitivity in the first forty minutes with animals subjected to various pressures. Thereafter the course plateaus

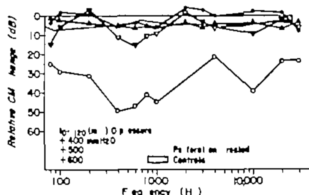


Fig 3 One μV CM difference scores at 0 pressure after 120 minutes of sustained positive pressure (individual Group I animals)

group Among these three groups of animals, there is a tendency for the higher pressures to have the greater effect on the mid and high frequencies The data was obtained from animals in Group I but the same relationship was observed in Group II animals

Fig 3 demonstrates the change in the one microvolt CM sensitivity following two hours of applied positive pressure (+400 to +600 mm H_2O) It is to be noted that the animal run at +600 mm H_2O developed a perforated tympanic membrane and had a loss as great as 50 dB at 400 Hz. A similar one microvolt CM contour was obtained for high negative perforating pressures as well In Fig. 3 the +600 mm H_2O animal may be compared to the control animal (no pressure applied) in which a perforation was created in the posterior aspect of the tympanic membrane Except for the

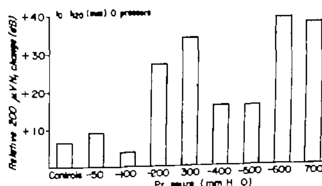


Fig 4 200 μV N_1 difference scores at 0 pressure after 120 minutes of sustained negative pressure (individual Group I animals).

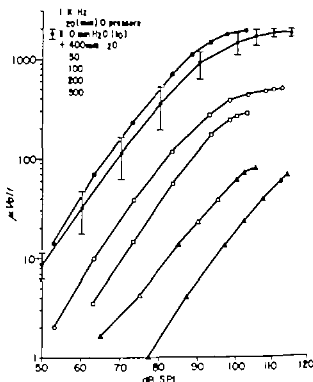


Fig 5 Input-output function at 0 pressure after 120 minutes of sustained pressure. Individual animals from Group II are compared to an initial mean curve at 0 pressure (two standard deviations are shown).

animals examined at pressures sufficiently high to cause drum membrane rupture the effect of positive pressure exposure was insignificant.

The N_1 data at zero pressure after 120 minutes of negative pressure exposure from −50 to −700 mm H_2O is shown in Fig. 4 Each bar represents individual animals from Group I There is a gradual decrease in sensitivity from −50 to −300 mm H_2O beyond which sensitivity either plateaus or becomes variable While this graph demonstrates individual Group I animals only similar results were noted in Group II animals as well

The input–output dynamic range at 1 000 Hz for one positive pressure animal and for four negative pressure animals is demonstrated in Fig. 5 The configuration of this input-output curve is similar for other frequencies tested as well. The negative pressure animals are in contrast to the animal run at +400 mm H_2O There is a definite decrease in sensitivity with increased negative pressure With greater nega

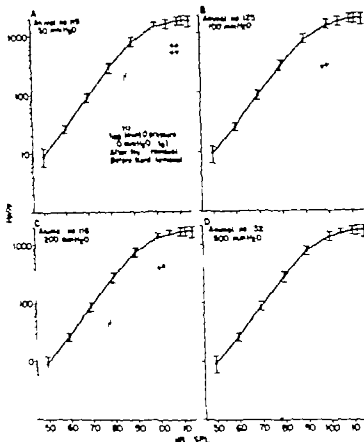


Fig. 11. Composite input-output functions at 0 pressure after 120 minutes of sustained pressure. Individual animals from Group II are shown before and after fluid removal.

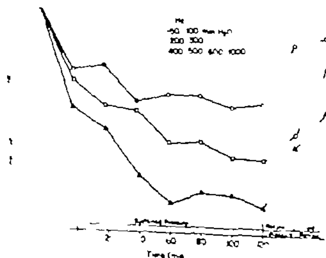


Fig. 12. Mean time course changes in the $1\ \mu V$ CM with sustained pressure for 120 minutes. Pressure is returned to 0 mm H_2O and fluid removed at the end. Time $\overline{T_0}$ and 0 mm H_2O is the reference (Group II animals).

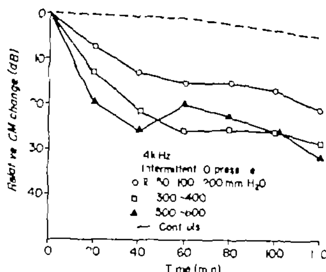


Fig 9 Mean time course changes in 0 pressure readings for the 1 μV CM during a 120 minute period of sustained negative pressure (Group II animals).

or is somewhat more variable In all frequencies tested −50 and −500 mm H_2O formed the two extremes at the end of 120 minutes Other pressures followed an intermediate course usually related to applied pressure, but an overlay of functions was noted [1]

Effect of fluid removal

Serous fluid and/or blood were noted in the middle ear of animals subjected to negative pressures When this fluid was removed at the end of each experiment (Group II animals) there was an overall improvement in the one microvolt CM of approximately 20 dB in the low frequencies 15 dB in the mid frequencies and 10 dB in the high frequencies. Furthermore as is shown in Figure 10 there is a difference in the mean improvement for the low frequencies (80 to 200 Hz) in animals run at pressures of −50 to −200 mm H_2O and the group of animals run at −400 to 600 mm H_2O For higher frequencies there does not appear to be a significant difference between these two groups

Effects of fluid removal on the dynamic range of the CM for Group II animals is shown in Fig 11 This composite figure of Group II

[1] Fig. 9 is based upon mean changes rather than individual observations due to the amount of individual variability which made the presentation of representative examples inappropriate

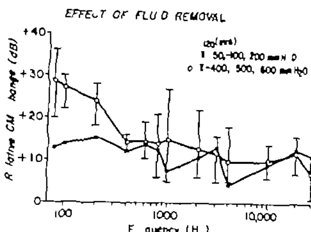


Fig 10 Mean improvement in the 1 μV CM resulting from fluid removal after 120 minutes of sustained negative pressure. The range as well as the mean is shown for the higher pressure group

animals includes data on individual subjects exposed to pressures of −50 to −500 mm H_2O The input-output function before and after fluid removal at 1 000 Hz is shown As can be seen from these graphs, there is a progressively greater effect from fluid as the pressure is increased up to −500 mm H_2O At −500 mm H_2O pressure, the effect of fluid removal is not much greater than that at −100 mm H_2O

At the end of each 120 minute pressure exposure an improvement in the one microvolt CM and N_1 response was seen when the system was returned to zero pressure and an additional improvement was noted when any existing fluid was removed These two findings are summarized in Fig. 12 for the one microvolt CM at 1 000 Hz over time This data is based upon observations in Group II animals The improvement in the CM for the animals tested between −50 and −100 mm H_2O is within 10 dB of normal while for the animals run at −200 to −300 mm H_2O the recovery was within 20 dB In the group with pressures above this level the recovery averaged 35 dB

Response to static pressure changes

Under constant stimulus conditions, the CM changes with different middle ear pressure The form of the CM change in normal guinea pigs is shown by the dashed line in Fig 13 This figure shows the changes in sound intensity

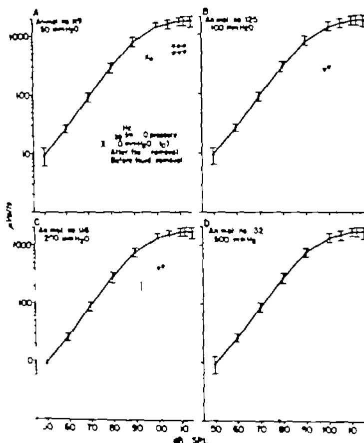


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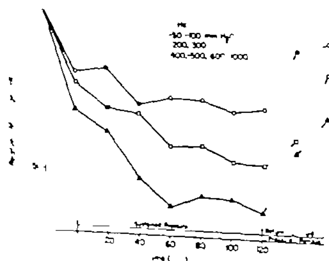


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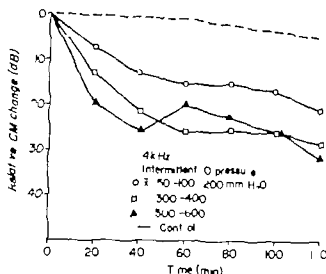


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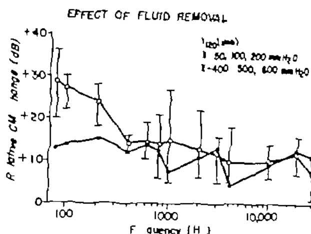


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Effect of fluid removal

Serous fluid and/or blood were noted in the middle ear of animals subjected to negative pressures When this fluid was removed at the end of each experiment (Group II animals) there was an overall improvement in the one microvolt CM of approximately 20 dB in the low frequencies 15 dB in the mid frequencies and 10 dB in the high frequencies. Furthermore as is shown in Figure 10 there is a difference in the mean improvement for the low frequencies (80 to 200 Hz) in animals run at pressures of 50 to −200 mm H_2O and the group of animals run at −400 to −600 mm H_2O For higher frequencies, there does not appear to be a significant difference between these two groups

Effects of fluid removal on the dynamic range of the CM for Group II animals is shown in Fig. 11 This composite figure of Group II animals includes data on individual subjects exposed to pressures of −50 to −500 mm H_2O The input-output function before and after fluid removal at 1 000 Hz is shown. As can be seen from these graphs, there is a progressively greater effect from fluid as the pressure is increased up to −500 mm H_2O At −500 mm H_2O pressure the effect of fluid removal is not much greater than that at −100 mm H_2O

At the end of each 120 minute pressure exposure an improvement in the one microvolt CM and N_1 response was seen when the system was returned to zero pressure and an additional improvement was noted when any existing fluid was removed These two findings are summarized in Fig. 12 for the one microvolt CM at 1 000 Hz over time This data is based upon observations in Group II animals The improvement in the CM for the animals tested between −50 and −100 mm H_2O is within 10 dB of normal while for the animals run at −200 to −300 mm H_2O the recovery was within 20 dB In the group with pressures above this level the recovery averaged 35 dB

Response to static pressure changes

Under constant stimulus conditions, the CM changes with different middle ear pressure. The form of the CM change in normal guinea pigs is shown by the dashed line in Fig. 13 This figure shows the changes in sound intensity

[1] Fig. 9 is based upon mean changes rather than individual observations due to the amount of individual variability which made the presentation of representative examples inappropriate.

HISTOPATHOLOGICAL OBSERVATIONS

General

The contrast injections were less successful than in previous studies where the middle ear had been opened and electrophysiological measurements and/or surgery performed on the cochlea but without any induced middle ear pressure changes (30, 31, 32). The most common finding was in fact an uninjected middle ear mucosa and a cochlea with contrast in only some modiolus vessels. In some cochleas, the blood was washed out by the saline perfusion, but no contrast had entered the vessels. In still others, the contrast filling was good in the middle ear mucosa and in the cochlear basal turn, with deficient vessel contrast apically. The outcome of the contrast injections appeared to be related to the type and magnitude of pressure. In animals which were assessed with positive and low negative pressures, the contrast injection was more successful than in those animals which were subjected to high negative pressures. The contralateral ears in general (18/22) showed the same amount of injected contrast as the experimental ear. In three cases, the contralateral ear was more contrast injected than the experimental ear and in one animal the opposite was found. On the whole, the middle ear changes were more consistent and more easily observed than the discrete cochlear morphological findings.

Table II *Present material. Histopathological examinations*

Middle Ear	Cochlea
Positive pressure	
5	4
Negative pressure (mm H_2O)	
Low (−50 to −100)	
4	2
Moderate (−300 to −400)	
6	3
High (−500 to −600)	
12	10
Pronounced (−800 to −1 000)	
3	2

Middle ear

The middle ear was examined for histopathological changes in thirty animals, distributed as demonstrated in Table II.

The *tympanic membrane* was *distended* in two of the positive pressure animals, in one of the low negative pressure animals and in all but two of all other negative pressure animals after two hours sustained pressure. In *one* animal from the pronounced negative pressure group where the drum membrane *did not* rupture, there was intra tympanic membrane hemorrhage as well as drum distention. The tympanic membrane was found to be *ruptured* in three of the five positive pressure animals, in one of the high negative and in two of the pronounced negative pressure groups. *Vessel distention* along the malleus was found in almost all animals (24 of 25 negative and 4 of 5 positive pressure animals) (Fig. 15). It thus appeared that most positive and negative middle ear pressures caused drum membrane distention and vessel dilation, and tympanic membrane rupture was related to the degree of pressure alone.

In three of five positive pressure animals and all negative pressure animals, the *middle ear* space contained serous fluid and/or hemorrhage. The middle ear contained *serous fluid* in two of the positive pressure animals, in all of the low and moderate negative pressure animals, and approximately half of the high negative pressure animals (8/15). *Hemorrhage* in the middle ear space was found in only two positive pressure animals but in most of the negative pressure animals (18/25) with greater frequency as the amount of applied negative pressure increased (Fig. 16). *Distention of middle ear mucosa vessels* was found in one of the positive pressure animals and in most of the negative pressure animals (22/25) (Figs. 16, 17). *Effusion of blood* around the vessel wall was found in 2 of 6 from the moderate negative pressure group, in 4 of 12 animals in the high negative pressure group and in 2 of 3 animals from the

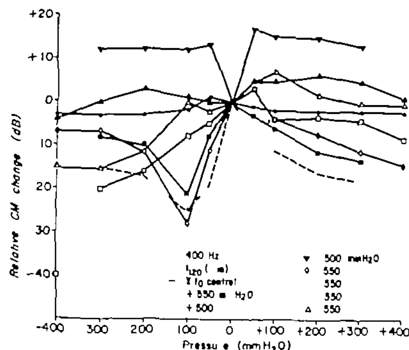


Fig 13 Comparison of the mean initial 1 μV CM response at time *T* with static pressure changes to the same responses after 120 minutes of high sustained pressure (individual animals from Group I).

for a 400 Hz tone necessary to hold CM amplitude constant (at one microvolt) as middle ear pressure was changed As middle ear pressure is varied from zero intensity of the sound must be increased[1] These data were *obtained in* animals prior to exposure to a longterm middle ear pressure change Following 120 minutes pressure exposure of ± 500 to ± 550 mm H_2O the response of the system to static middle ear *pressure changes (solid lines in Fig. 13) Follow*ing a two-hour exposure, the system responds to middle ear pressure change from levels similar to the pre-exposure response to the extreme where changes in middle ear pressure actually *increase the response of the cochlea to sound* The effect was not correlated with direction of pressure change or fluid buildup in the middle ear space It did appear correlated to drum membrane flaccidity

Fig. 14 shows the change in the one microvolt CM for zero pressure following a 120 minute period of sustained pressure. In addition these results are compared with three locations of intracochlear bleeding in nine animals. The animals used in this figure were from both Group I (four animals) and Group II (five animals) Average pressure variations were -500 mm H_2O and -630 mm H_2O A 20 dB difference across frequencies between those *animals with scala tympani hemorrhage and* the animals with both scala tympani and scala vestibuli hemorrhage was noted With scala vestibuli alone an intermediate decrease in CM sensitivity was observed.

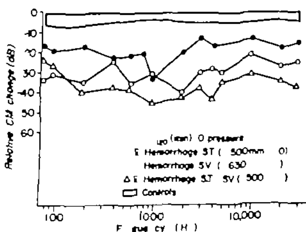


Fig 14 Mean 1 μV CM difference scores at 0 pressure after 120 minutes of sustained pressures for groups of animals with scala tympani (ST), scala vestibuli (SV) and both scala tympani and scala vestibuli (ST SV) hemorrhages respectively Four animals from Group I and five from Group II

[1] These data agree approximately with those reported in the literature by Wever et al (18, 28 29).




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16




17

pronounced negative middle ear pressure group (Figs. 16, 17) *Engorgement of bone vessels* with blood was found in two of the positive animals and in 4 of 15 animals exposed to negative pressure greater than −500 mm H_2O (Figs. 16 and 18)

It thus appears that *positive pressure* influences the middle ear mucosa with only occasional transudation of serous fluid and hemorrhage as well as bone vessel engorgement With *negative pressure* a regular finding is transudation of serous fluid as well as distended middle ear mucosal vessels With more pronounced negative pressure blood can also be found surrounding the vessel wall as well as free hemorrhage in the middle ear space. In no case was any luxation or displacement of middle ear ossicles observed

Cochlea

Histopathological studies of the inner ear were made in one control animal (created tympanic membrane perforation) and 21 animals distributed as demonstrated in Table II *The round and oval window membranes* were found to be *intact in all animals Similarly in no case* were any histopathological changes demonstrated in the *Organ of Corti* or in the *endolymph* Contrarily *hemorrhage in perilymph* was the most distinctive pathological inner ear finding (Fig. 19) *Hemorrhage was found in all animals* except those in which the tympanic membrane ruptured and in two animals in the low negative pressure group Of those in the positive pressure group one demonstrated a discrete hemorrhage in both scala vestibuli and scala tympani of the basal turn. In another animal a more pronounced hemorrhage was found in the apical turn in scala vestibuli, decreasing basally In this animal there was also found a scala tympani hemorrhage in the second turn Two positive pressure animals without cochlear hemorrhage had ruptured tympanic membranes. In three moderate negative pressure animals one animal exhibited a small hemorrhage most apparent in the basal turn close to the round window in the scala tympani (Fig. 20), another showed hemorrhage in the scala vestibuli in the first and third turn, and the third had hemorrhage in both scala vestibuli and scala tympani in the basal and second turns.

In the high negative pressure group hemorrhage in the perilymph was found in eight animals. In three cases a pronounced hemorrhage was found in the scale tympani close to the round window In two animals, a discrete hemorrhage was found in the scala vestibuli, in one of them in the basal turn, another in the third turn. In three animals hemorrhage was found in both scala vestibuli and scala tympani In two of those it was limited to the basal turn and in the third animal most pronounced apically and decreasing basally One of the animals in the pronounced negative pressure group showed hemorrhage in the scala vestibuli of the basal turn.

Hemorrhage was never found in the cochleas with a ruptured tympanic membrane. Only in one case could the hemorrhage be related to a ruptured vessel In one animal (~400 mm H_2O) the "suspension vein" going from the modiolus in the basal turn close to the round window and running free through perilymph to the external wall, was found to be ruptured with hemorrhage. Interestingly in the same animal the control ear showed a similar hemorrhage and a ruptured suspension vein"

Granulated material appearing as debris rather than protein casts was found in three animals,

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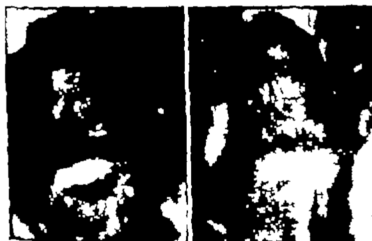
Fig 15 Tympanic membrane of a control animal (left) and after 120 minutes of sustained negative pressure (right). Vessel distention is easily observed along the malleus.

Fig 16 Guinea pig cochlea after 120 minutes of sustained negative pressure −200 mm H_2O (left) and −50 mm H_2O (right). The middle ear mucosa shows vessel distention and hemorrhage (left) whereas the bone vessels appear engorged with blood (right).

Fig 17 Guinea pig cochlea after 120 minutes of sustained negative pressure (−1 000 mm H_2O). The contralateral ear (left) shows normal ingestion of contrast in middle ear mucosa vessels covering the cochlea. No contrast has entered the vessels in the pressurized middle ear vessels (right) which appear dilated, engorged by blood and with hemorrhage i the middle ear space.



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Fig 15 Tympanic membrane of a control animal (left) and after 120 minutes of sustained negative pressure (right). Vessel distention is easily observed along the malleus.

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Fig 17 Guinea pig cochlea *after 120 minutes of sustained* negative pressure (−1 000 mm H_2O). The contralateral ear *(left) shows normal ingestion of* contrast *J* middle ear mucosa vessels covering the cochlea No contrast has entered the vessels *I the pressurized middle ear vessels (right) which appear* dilated, engorged by blood *and with hemorrhage* in the middle ear space.



Fig. 15. Guinea pig cochlea after 120 minutes of sustained negative pressure (−500 mm H_2O). Vessels in the bone surrounding the cochlea appear somewhat dilated and engorged with blood.

two in the high negative pressure group and one in the pronounced high negative pressure group. In all cases the debris was located in the scala tympani close to the round window and found in addition to hemorrhage.

Small *bubbles* formed in the perilymph of the scala tympani were found in one positive and one negative pressure animal. *Distortion (or collapse) of the vestibular membrane* was found in one of the positive pressure animals, in two low negative pressure animals, in six of twelve animals in the high negative pressure group and in both animals in the pronounced negative pressure group (Figs. 18, 21). In general the distention or collapse was found throughout the cochlea.

Common findings in all groups were *pigment anomalies in the stria vascularis* with uneven distribution of pigment often markedly distributed around the vessel walls.

Other pathological findings included a few cases in which the surface cells of the stria vascularis appeared degenerated. In these preparations many vessels were completely uninjected and many were missing. In most of these cases of strial degeneration, similar findings were made in the control ear. Further in addition to the stria vascularis changes, an increased number of *phagocytes (melanocytes)* was often found located along the vessel(s) of the spiral prominence. In a single animal from the low negative middle ear pressure group some injected contrast was found outside the collecting venules of the scala tympani. However a similar finding was made in the control ear in three different locations. Further this animal showed the most pronounced apical stria atrophy of all animals.

In conclusion, in all animals (except the low negative pressure animals) in which the tympanic membrane did not rupture, hemorrhage was found in the inner ear. In two animals hemorrhages were demonstrated bilaterally. The blood was most commonly demonstrated in the scala

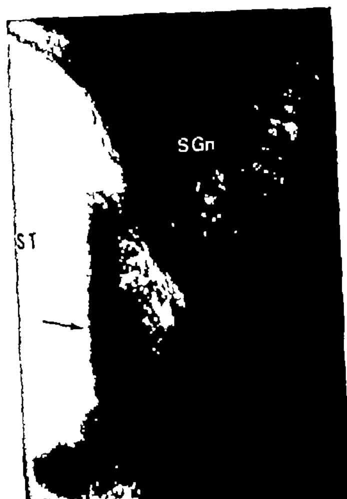


Fig. 20. Guinea pig cochlea after 120 minutes of sustained pressure (400 mm H_2O). The most common site of hemorrhage (arrow) was in the scala tympani (ST) close to the round window. Spiral ganglion = SGn.

Control animal

Morphological experiences from several hundred guinea pigs served as controls for this project. The surgical procedure for these animals was described above. All animals showed a small amount of serous fluid in the middle ear. In the animal with a surgically created perforation the middle ear showed distended vessels in the mucosa and a small hemorrhage. The cochlea was well injected by contrast in the two basal turns. There was some debris inside the round window and some pigment anomaly of the stria vascularis.

In all animals, the contralateral unassessed ear served as a control. The examination was made in a similar fashion as in the experimental ear. Frequent findings were distention and collapse of the vestibular membrane, pigment anomalies of the stria vascularis, and an increased amount of melanocytes in the spiral prominence.



Fig 19 Guinea pig cochlea after 120 minutes of sustained negative pressure (−400 mm H_2O). *Localized hemorrhage* is seen in the scala tympani of the basal turn close to the modiolus. Considerable distention of the vestibular membrane is also observed.

tympani of the basal turn close to the round window often appearing to be sealed and situated at the modiolus wall *In some other* cases the hemorrhage was more diffuse and most prominent at the external wall. The hemorrhage often appeared to be adjacent to the opening of the cochlear aqueduct In four cases an accumulation of cellular white colored material was demonstrated (debris?) always situated in the scala tympani close to the round window *In three of these cases hemorrhage* was also found in the perilymph of the same ear The origin of the hemorrhage could in one case be related to the "suspension vein" which was broken and surrounded by an accumulation of red blood corpuscles In most ears with perilymphatic hemorrhages the "suspension vein if pres nt was intact

In no case was any rupture of the round window membrane, any hemorrhage in the endolymph, or any changes in the Organ of Corti observed In no case with tympanic membrane perforation was any cochlear hemorrhage demonstrated

Common findings were distended and collapsed parts of the vestibular membrane and a *nicking and splitting up of the peripheral parts* of the basilar membrane (Fig 21). However such findings were also made in the contralateral ear There was no difference in the morphological findings of the middle ear and cochlea in animals from Groups I and II

change in the one microvolt CM contour N_1 response and CM dynamic range. When middle ear hemorrhage was present, not only was there a large effect on cochlear potentials, but failure to improve following fluid and blood removal was also noted. This observation agrees with the clinical finding that hearing loss in middle ear barotrauma is frequently not noted until hemorrhage is present (16).

Changes in elastic properties of the tympanic membrane and the middle ear transmission mechanism were apparent, although not quantitatively measured in this study. With higher pressures, distention and hypermobility of the tympanic membrane were seen, reflecting a change in tympanic membrane elastic properties. In addition, the decreasing cochlear output recorded over time with zero pressure readings as well as with sustained pressure readings suggest that changes in elastic properties of the middle ear have occurred. We suggest this conclusion is further indicated by the observations made in Fig. 13 in which the response of the system following pressure exposure was markedly affected. This data indicates that in some instances middle ear pressure exposure may change the elastic characteristics of the drum sufficiently to actually reduce its effective surface area in receiving sound energy. However when positive or negative middle ear pressure is then reapplied to such a traumatized tympanic membrane its effective vibrating surface is restored with resultant improvement of the cochlear output.

The exact extent to which tympanic membrane perforations contribute to cochlear output change in our animal model is not clear. As noted in Fig. 3, a decrease in sensitivity of 50 dB in the one microvolt CM was found in the low and mid frequencies for a high positive pressure animal in which a tympanic membrane perforation was present. The results shown in Fig. 7 may be interpreted to indicate that this pressure induced perforation caused a sudden change in the recorded cochlear potential. Similar losses in the cochlear potential were also observed for high negative pressure animals with tympanic membrane perforations and with middle ear fluid. A loss of 50 dB in cochlear output is more than has been reported in human patients sustaining barotraumatic perforations, where losses on the order of 5 to 15 dB are observed (16, 33). These smaller losses agree somewhat more closely with that of one control animal in which a perforation was surgically made in the drum membrane and no fluid demonstrated. Consequently, we suggest that larger loss may in part be due to middle ear hemorrhage or fluid in addition to the perforation. Using a similar guinea pig model, we found only 30 dB loss across frequencies with tympanic membrane perforations caused by abrupt phasic pressure changes (from +1 000 to +5 000 mm H_2O) where fluid accumulation was not seen.

Interpretation of the relationship between inner ear hemorrhage and decreased cochlear function is not clear because cochlear changes take place simultaneously with middle ear histopathological changes. Also by using round window electrode recordings, it is not possible to localize the effects of discrete cochlear lesions accurately. Nevertheless, when the areas of intracochlear hemorrhage were compared there was a marked difference in the one microvolt CM response when hemorrhage was present in both scala tympani and scala vestibuli as compared to hemorrhage in scala tympani or scala vestibuli alone.

HISTOPATHOLOGICAL ASPECTS

In general, histopathological middle ear changes were consistent with previous findings in middle ears subjected to aural barotrauma (8, 12, 13, 14, 15, 16). The most important and conclusive findings of this investigation were the normal appearance of the round window, endolymph, Organ of Corti, and the high frequency of perilymphatic hemorrhages. The demonstration of round window membrane ruptures or oval window fistulas in the human ear under diving conditions (5, 35, 36, 37) could not be confirmed under the present experimental conditions. This may be due to a species difference in the



Fig 21 Guinea pig cochlea after 120 minutes of sustained negative pressure. There is pronounced distention of the vestibular membrane. The basilar membrane appears nicked in the basal direction. Other structures appear normal.

Discussion

ELECTROPHYSIOLOGICAL ASPECTS

Changes in cochlear electrophysiological responses were noted to be both time and pressure related In general there was a gradual decrease in the one microvolt CM and N_1 functions with time These changes were observed to be directly related to increasing pressure Little difference between those animals subjected to 120 minutes of sustained pressure (Group I) and those with interrupted zero pressure readings (Group II) was observed This indicates that the dynamic changes in pressure in Group II cannot account for the electrophysiological findings of this study Instead the functional changes are the result of the sustained middle ear pressure, and dependent both upon duration and amplitude.

The physiological changes were clearly related to fluid accumulation in the middle ear However with increasing pressure other factors may contribute to the greater loss of cochlear response e g changes in the elastic properties of the tympanic membrane, middle ear transmission mechanism, tympanic membrane perforations, and the presence of middle and inner ear hemorrhage.

As expected, middle ear fluid and hemorrhage were predominant in negative pressure animals and the amount and occurrence correlated with the degree of pressure applied The observation that fluid influences the ossicular chain (12, 16, 33) was substantiated by the present investigation. The effects of fluid removal are greater for the lower frequencies where middle ear mechanisms play a major role in sound transmission

In general, the higher negative pressure animals demonstrated a greater amount of middle ear hemorrhage than the lower pressure animals. Such animals exhibited the greatest

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Discussion

ELECTROPHYSIOLOGICAL ASPECTS

Changes in cochlear electrophysiological responses were noted to be both time and pressure related. In general, there was a gradual decrease in the one microvolt CM and N_1 functions with time These changes were observed to be directly related to increasing pressure. Little difference between those animals subjected to 120 minutes of sustained pressure (Group I) and those with interrupted zero pressure readings (Group II) was observed This indicates that the dynamic changes in pressure in Group II cannot account for the electrophysiological findings of this study Instead the functional changes are the result of the sustained middle ear pressure, and dependent both upon duration and amplitude.

The physiological changes were clearly related to fluid accumulation in the middle ear However with increasing pressure other factors may contribute to the greater loss of cochlear response, e.g., changes in the elastic properties of the tympanic membrane middle ear transmission mechanism, tympanic membrane perforations, and the presence of middle and inner ear hemorrhage.

As expected middle ear fluid and hemorrhage were predominant in negative pressure animals and the amount and occurrence correlated with the degree of pressure applied. The observation that fluid influences the ossicular chain (12, 16 33) was substantiated by the present investigation The effects of fluid removal are greater for the lower frequencies where middle ear mechanisms play a major role in sound transmission.

In general, the higher negative pressure animals demonstrated a greater amount of middle ear hemorrhage than the lower pressure animals Such animals exhibited the greatest

bution of different frequencies of stimulation to the response of the cochlea. On the basis of a study performed by one of the authors (Mc Pherson, 29) we do suggest that for the recording of cochlear microphonic activity to stimuli above a frequency of approximately 2 000 Hz the round window provides an adequately sensitive recording site. Recordings from this site, however cannot be expected to be sensitive to restricted differential changes in responsiveness occurring along the Organ of Corti (39 40)

In regard to histopathology there are a number of specific observations reported in this paper which should be viewed with the technical approach and animal model we used well in mind. It appears that the present material is often afflicted by cochlear pathology presumably without relation to the induced middle ear pressures. In one animal which was to be included, no electrophysiological measurements could be obtained. This cochlea demonstrated a severe degeneration of all intracochlear structures The most common pathological findings were pigment abnormalities in the stria vascularis and an increased number of melanocytes in the spiral prominence and in the vestibular membrane, particularly at the attachment of the external wall. These changes may indicate aging or other degenerative processes or genetic characteristics

In many cases, the inspection of the middle ear through the otomicroscope at the end of the two-hour experimental period did not disclose any middle ear hemorrhage However later hemorrhages were found in the middle ear and could have at times been caused by widening of the bulla hole that was made in order to inspect the ossicles and the round and oval windows at the end of the experiment. On the other hand, obviously minor hemorrhages could have been missed during the inspection made through the small bulla hole

The occurrence of blood in the contralateral cochlea of two guinea pigs where hemorrhage was also found in the experimental ear is difficult to explain but may be due to technical reasons. Such inner ear hemorrhages have also been encountered occasionally in previous experiments and may besides being induced by technical deficiencies, also reflect an occurrence of spontaneous hemorrhage in the inner ear of the guinea pig.

By comparison with other pathological investigations (30 31 32) perfusion and intravascular injection of the middle ear and cochlea of these animals was far less successful. This appears to be the result of the pathological variable middle ear pressure exposure, rather than to electrophysiological recordings and preparation. We did not see as many problems with vascular perfusion in other longterm electrophysiological preparations. It must be pointed out, however that our previous experiences with animals in which any kind of assessment of the middle or inner ear is made leads to a less favorable outcome of subsequent contrast injection when compared with normal intact preparations. A frequent unexpected finding in this regard was the observation that many control ears were also poorly injected. In most cases, there was a very close correlation between the experimental and the control ear There was a correlation between amount of pressure that the animal was exposed to and the outcome of the perfusion in both ears. These observations suggest that exposure to two hours of middle ear pressure may have a general systemic effect on the vasculature (possibly mediated via the autonomic nervous system). The occurrence of contrast in the vessels is by no means necessary for the interpretation of cochlear vascular pathology With phase contrast microscopy the vessels including the lumen and wall are still easily observable. It is interesting to note that in the present investigation pathological findings were already observed on the longitudinally sectioned surface of the cochlea after decalcification. The section was carefully made, usually in the baso-apical direction with a sharp razor blade. In the early experiments the fixative was injected through the cochlear windows and apex. This and the subsequent sectioning of the cochlea may all have influenced the integrity of the vestibular and basilar membranes. Consequently

middle ear dynamics between man and guinea pig.

The occurrence of inner ear hemorrhage is consistent with previous experiments (24 38). The origin of hemorrhage is an unanswered question Only in a single case could the hemor rhage be related to a particular vessel In no case was a hemorrhage related to any injected contrast outside vessels or to an observed rupture of vessels. It was most commonly demonstrated in the scala tympani close to the round window and in the immediate neighbor hood of the cochlear aqueduct It may be that the hemorrhage either originated from cochlear aqueduct or was on its way in the opposite direction "to be drained" via the cochlear aqueduct.

A correlation between increased middle ear pressure and cochlear hemorrhage was clearly shown Further these animals without inner ear hemorrhage showed consistent findings compatible with a low middle ear pressure i e four had a tympanic membrane perforation, and two animals belonged to the lowest negative pressure group (−50 −100 mm H_2O) Therefore the absence of cochlear hemorrhage empha sizes the relation of middle ear pressure and inner ear histopathology It appears that high pressure may cause either a tympanic membrane perforation or an inner ear hemorrhage The absence of round window perforations indicates a greater round window membrane resistance to pressure trauma than for the tympanic membrane in the guinea pig.

It is obvious that forces which may induce cochlear hemorrhages also may distend and rupture delicate membranes of the inner ear In this connection, it may be emphasized that the vestibular membrane appears to be quite elastic and distends greatly before rupturing. A moderate distention or collapse of the vestibular membrane was a frequent finding in the present investigation With the present technical approach it is impossible to determine whether this was due to applied middle ear pressure or to the technical assessment of the cochlea or both In some instances, however the distention of the vestibular membrane was very marked (Fig. 21) which could hardly be explained by any of the technical procedures involved One additional weak spot in the cochlea appeared to be the basilar membrane i e the zona pectinata The common nicking of this part of the cochlea and splitting up of the layers (Fig. 21) may again be due to the technical assessment or to the pressure changes Even if this nicking can be explained by the histological procedures as evidenced by similar but less marked nicking in the control ear this area of the basilar membrane appears to be a vulnerable site in the cochlea for different kinds of trauma.

In two cases, one with high positive pressure and one with moderate negative pressure, small "bubbles were found in the inner ear It must be emphasized that discrete bubbles located at sites in the cochlea other than near the round window membrane could not have been observed with the present approach. The occurrence of bubbles" may consequently have been higher than was found We have no suggestions regard ing the origin of these bubbles

TECHNICAL CONSIDERATIONS

In evaluating the observations made in this study and interpreting their significance, certain technical considerations must be kept well in mind In regard to the electrophysiological observations, the reservations are basically two (1) the use of anesthesia and (2) the use of round window recording procedures. The use of anesthesia is of course an undesirable albeit appropriate, requirement of such investigations. Physiological evidence indicates that anesthetics effect on the receptor electrophysiological re sponsiveness may not be great (25)

In regard to the round window recordings it might be suggested that these are not as sensitive to changes occurring at the apex of the cochlea as they are to changes occurring at the base close to the recording electrode Thus, changes in response to high and low frequency stimuli may have been differentially recorded However presently it is not possible to evaluate the contri

ings include the interesting observation of an intact round window membrane, a clear endolymph, and a normal Organ of Corti in all cases. Positive findings were a high frequency of hemorrhage, most commonly demonstrated in the scala tympani of the basal turn close to the round window. The origin of the hemorrhages could not be demonstrated with the present investigation. The hemorrhages often appeared to be related to the cochlear aqueduct. The occurrence of hemorrhage was clearly related to increased negative pressure and the non-existence of hemorrhage was always related to either tympanic membrane perforations or low applied pressure. Further frequent findings were distention, collapse, and rupture of the inner ear membranes which must be interpreted with great circumspection due to the method used. Likewise, some of the pathological cochlear findings may be due to pathological conditions which are not necessarily related to induced middle ear pressure.

Acknowledgements

This work was supported in part by a contract the Office of Naval Research (N00014-67 A 0103-0031) and by research and training grants from the U.S. Public Health Service (PE 00190) and the National Institutes of Health (IT1 NBO-5553 and R01 NS 08181-04). We also wish to acknowledge the technical and editorial assistance of Mr Björn Larsson and Mrs. Mary Bartoo.

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when abnormalities in these membranes were found the injection of fixative was abandoned and the cochleas immersed in the fixative. However we still feel that deviations of these membranes from a normal position must be interpreted with great circumspection Since the Organ of Corti was in all cases found to be normal it may be suggested that in future experiments of the same kind openings of the cochlea for fixative purposes should be limited to the round and oval windows.

Interpretation of distortion and changes in the membranes within the cochlea is difficult with this or any other histological approach that we have been able to think of Possibly the conventional temporal bone embedding procedure is the only one available which may not immediately influence the cochlear membranes Although these reservations are serious control observations did not show such pronounced changes in the position of the membranes of the labyrinth Consequently similar to the deficient vascular contrast injection the changes in membrane position may indeed be the result of this longterm middle ear pressure exposure

CLINICAL ASPECTS

It is obviously tempting to make comparisons between the present experiment and the situation of the human in diving conditions. However simultaneously many concerns arise in doing so with respect to the difference of the experimental approach to the middle ear biological differences etc Further in the human diver another factor influences both the middle and inner ear i.e., the ability to equalize pressure This factor was kept stable in the present experiment, i.e no equalization of middle ear pressure was achieved spontaneously In this respect the experimental model may be considered to be similar to the diver who cannot perform the Valsalva maneuver The middle ear findings tend to substantiate previous findings of aural barotrauma in the human very closely The inner ear findings, however did not confirm previous findings of window membrane rupture They tend more to correlate with previous findings of sudden inner ear membrane breaks (41 42) It may be suggested from the findings of the present investigation that inner ear hemorrhage is an alternative explanation for sudden hearing loss in connection with diving Further it is felt that similar to the healing of inner ear membrane breaks this hemorrhage may be absorbed or drained with a final recovery of hearing. From the present experiment it would appear that the cochlear aqueduct takes a great part in the clearing of the scala tympani perilymph. This hypothesis is also supported by other previous investigations (43 44 45)

Summary

The electrophysiological findings show a time and pressure related decrease in function of the CM and the N_1 potentials. Sudden changes were correlated with tympanic membrane perforations Some of the decreased function is accounted for by middle ear effusion and hemorrhages, reducing mechanically the transmission of sound energy through the middle ear This was evidenced by an improvement of function when the fluids were removed Remaining decreases in function were interpreted as a result of influences on the inner ear function or of undisclosed middle ear changes. No differences were noted in cochlear function between animals subjected to sustained or intermittent middle ear pressures. Neither were any morphological differences noted between these two groups in the middle or inner ear

The morphological middle ear findings correlated well with previous clinically and experimentally induced changes with increased/decreased middle ear pressure The cochlear find

ings include the interesting observation of an intact round window membrane, a clear endolymph, and a normal Organ of Corti in all cases. Positive findings were a high frequency of hemorrhage, most commonly demonstrated in the scala tympani of the basal turn close to the round window. The origin of the hemorrhages could not be demonstrated with the present investigation. The hemorrhages often appeared to be related to the cochlear aqueduct. The occurrence of hemorrhage was clearly related to increased negative pressure, and the non-existence of hemorrhage was always related to either tympanic membrane perforations or low applied pressure. Further frequent findings were distention, collapse, and rupture of the inner ear membranes which must be interpreted with great circumspection due to the method used. Likewise, some of the pathological cochlear findings may be due to pathological conditions which are not necessarily related to induced middle ear pressure.

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Address for reprint

A Axelsson, M.D
Dept of Audiology
Sahlgrenska sjukhuset
S-413 45 Göteborg
Sweden

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SUPPLEMENT 336

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The fine structure of freeze-fractured intercellular junctions in the guinea pig inner ear

KLAUS JAHNKE

From the Department of Otorhinolaryngology University of Cologne, Germany
(Head Prof Dr Dr F Wustrow) and the King Gustaf V Research Institute,
Laboratory for Electron microscopy of the Department
of Otorhinolaryngology Karolinska Sjukhuset, Stockholm, Sweden
(Head Prof. Dr J. Wersäll)

TO MY WIFE

Gesamtherstellung H Laupp jr Tübingen
1975

CONTENTS

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I Introduction

Many experiments have shown (see Dallos, 1973) that the functions of the inner ear are intimately connected with the unique ion composition of the endolymph, which is characterized by very high potassium and very low sodium concentrations (Smith et al., 1954) The maintenance of these ion concentrations essentially depends on the structure and functional integrity of the plasma membranes of those cells, which represent the barriers between the different inner ear compartments (1) endolymphatic space, (2) perilymphatic spaces, (3) intercellular spaces of the stria vascularis. The same is true for the maintenance of the resting potentials of the inner ear which were first described by von Bekesy (1952) and also for the ability of the inner ear hair cells to develop receptor potentials. It is established that the epithelial cells and their zonulae occludentes (Farquhar and Palade, 1963) lining the endolymphatic space constitute the perilymph endolymph-barrier (see Jahnke, 1973)

The freeze-etch technique has become an important investigative method in studying the fine structure of biological membranes. In the freeze fracture process the fracture occurs through the hydrophobic core of the membrane (Branton, 1966), exposing two intramembranous fracture faces the fracture face A adjacent to the cytoplasm, and the fracture face B adjacent to the extracellular space. Both fracture faces show globular particles of [illegible]riable sizes which are believed to be proteins and lipoproteins (Boetscher 1973; Packer 1974). They are cytoplasmically synthesized and swim in the phospholipid bilayer (fluid mosaic model of Singer and Nicolson, 1972) The intramembranous particles are preferentially associated with the A fracture face.

Intercellular junctions are also split by freeze fracture revealing their internal macromolecular architecture. Thus zonulae occludentes exhibit the presence of a branching and anastomizing network of ridges on the A fracture face and a complementary network of grooves on the B fracture face (Kreutziger 1968 Staehelin et al., 1969) There is evidence that the fibrils of the network are the sealing component of the junction (Goodenough and Revel, 1970 Friend and Gilula, 1972) In a recent paper a single fibril model for the zonula occludens was proposed (Wade and Karnovsky 1974 a)

The purpose of this paper is to describe the distribution, size and configuration of freeze-fractured intercellular junctions of the perilymph-endolymph barrier with special reference to the plasma membrane structures of the inner ear sensory epithelia. It includes the results of an examination of freeze fractured inner ear synaptic membranes. A preliminary report of freeze-fracturing of cochlear tissues has appeared elsewhere (Jahnke, 1974)

The freeze-etched fine structure of the stria vascularis has previously been reported in detail (Jahnke, 1975).

II Material und Methods

14 pigmented guinea pigs (6 male, 8 female), weighing [illegible]35–360 g, were anesthetized by intraperitoneal injection (30–35 mg/kg body weight) of Nembutal sodium The right cochlea of 9 animals was exposed, and a hole was made in its apex, and then both the oval and the round window were opened.

Subsequently the cochlea was perfused with 2% paraformaldehyde 2,5% glutaraldehyde in 0 1 M cacodylate buffer (pH 7 4) for 5–10 min. Following decapitation the temporal bones were removed and dissected The inner ears remained in identical aldehyde solutions for 2 hours at 0–4 C, and were carefully washed and stored in 0 1 M cacodylate buffer The tissue was then soaked in 20% glycerol in 0 1 M cacodylate buffer Tissue from 8 animals was glycerinated without the use of chemical fixatives.

Small dissected specimens from the cochlear duct the saccule the utricule and the cristae ampullares were rapidly frozen in liquid freon 22 cooled by liquid nitrogen. The tissue was fractured and etched (1 min) in a Balzers freeze-etch unit BA 360 M (Balzers AG Liechtenstein) at −100° C. The platinum-carbon replicas were picked up on uncoated grids or formvar membranes and examined with either a Siemens Elmiskop 101 A or a Siemens Elmiskop 1 A at 80 kV

III The perilymph-endolymph-barrier of the cochlea and the compartment of the stria vascularis

A OBSERVATIONS

In order to study the structures which surround the cochlear duct small tissue pieces of all coils were oriented before freezing so that the fracture plane would occur as the usual midmodiolar sections. Frequently some parts were fractured as expected, while in other regions the fractures were oblique to various degrees. The following description is based on the evaluation of aldehyde-fixed tissue compared with unfixed. Only small differences were noted. Generally the fracture plane was more uneven in nonfixed tissue particularly in the region of intercellular junctions. This finding agrees with the report by Staehelin (1973) Descriptions of membrane particle densities are based on fixed specimens although considerable differences in the densities of intramembranous particles (Kirk and Tosteson 1973 McIntyre et al., 1974) were not noted in unfixed inner ear cell membranes. Freeze

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Fig 1 Freeze-etched Reissner s membrane. On the left the cochlear duct (CD) and on the right the scala vestibuli (SV) The cytoplasm of the epithelial cells is crossfractured. Fracture faces of Golgi apparatus (Ga) endoplasmic reticulum (eR) and some vesicles (v) can be seen. A micropinocytotic vesicle (arrow) fuses with the basal cell membrane face. There are a few particles on the B fracture faces (B) and some more on the A fracture faces (A) of the microvilli The zonula occludens (zo) sealing the cochlear duct is obliquely fractured and exhibits a small region of it s B face M = mesothelial cell. × 32.000.

Fig 2 Reissner s membrane The freeze-fractured zonula occludens is seen as a series of ridges of about 90 Å diameter on the A fracture face (A) and a series of complementary grooves on the B fracture face (B) It is composed of usually four to eight but sometimes more interconnected strands in Reissner s membrane as well as in other nonsensory epithelia lining the endolymphatic space There is a moderate number of particles on the apical (a) and on the lateral (l) membrane A fracture face CD = cochlear duct cy = cytoplasm of the epithelial cell which was detached by freeze fracturing. × 90.000.

Fig 3 Freeze-etched outer sulcus epithelium. Characteristic fracture of a zonula occludens (zo) with on the A fracture face about seven horizontal ridges, which seal the cochlear duct (CD) The A fracture faces (A) of the microvilli exhibit many particles, whereas on the B fracture faces (B) only a few can be detected. × 25 000.

The arrowhead below right indicates direction of platinum shadowing. The freeze-etch illustration should be viewed from that direction.

When unfixed specimens are shown this will be specified.

Subsequently the cochlea was perfused with 2% paraformaldehyde, 2,5% glutaraldehyde in 0,1 M cacodylate buffer (pH 7 4) for 5–10 min. Following decapitation the temporal bones were removed and dissected. The inner ears remained in identical aldehyde solutions for 2 hours at 0–4 C, and were carefully washed and stored in 0 1 M cacodylate buffer The tissue was then soaked in 20% glycerol in 0 1 M cacodylate buffer Tissue from 8 animals was glycerinated without the use of chemical fixatives.

Small dissected specimens from the cochlear duct, the saccule the utricule and the cristae ampullares were rapidly frozen in liquid freon 22 cooled by liquid nitrogen. The tissue was fractured and etched (1 min) in a Balzers freeze-etch unit BA 360 M (Balzers AG Liechtenstein) at −100° C. The platinum-carbon replicas were picked up on uncoated grids or formvar membranes and examined with either a Siemens Elmiskop 101 A or a Siemens Elmiskop 1 A at 80 kV

III The perilymph-endolymph-barrier of the cochlea and the compartment of the stria vascularis

A OBSERVATIONS

In order to study the structures which surround the cochlear duct small tissue pieces of all coils were oriented before freezing so that the fracture plane would occur as the usual midmodiolar sections. Frequently some parts were fractured as expected, while in other regions the fractures were oblique to various degrees. The following description is based on the evaluation of aldehyde fixed tissue compared with unfixed. Only small differences were noted. Generally the fracture plane was more uneven in nonfixed tissue particularly in the region of intercellular junctions. This finding agrees with the report by Staehelin (1973) Descriptions of membrane particle densities are based on fixed specimens although considerable differences in the densities of intramembranous particles (Kirk and Tosteson, 1973 McIntyre et al., 1974) were not noted in unfixed inner ear cell membranes. Freeze

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Fig 1 Freeze-etched Reissner s membrane. On the left the cochlear duct (CD) and on the right the scala vestibuli (SV) The cytoplasm of the epithelial cells is crossfractured. Fracture faces of Golgi apparatus (Ga), endoplasmic reticulum (eR) and some vesicles (v) can be seen. A micropinocytotic vesicle (arrow) fuses with the basal cell membrane face. There are a few particles on the B fracture faces (B) and some more on the A fracture faces (A) of the microvilli. The zonula occludens (zo) sealing the cochlear duct is obliquely fractured and exhibits a small region of it s B face. M = mesothelial cell. × 3_000.

Fig 2. Reissner s membrane The freeze-fractured zonula occludens is seen as a series of ridges of about 90 Å diameter on the A fracture face (A) and as a series of complementary grooves on the B fracture face (B) It is composed of usually fo r to eight but sometimes more interconnected strands in Reissner s membrane as well as in other nonsensory epithelia lining the endolymphatic space. There is a moderate number of particles on the apical (a) and on the lateral (l) membrane A fracture face. CD = cochlear duct, cy = cytoplasm of the epithelial cell, which was detached by freeze fracturing × 90 000.

Fig 3 Freeze-etched outer lcus epithelium. Characteristic fea ture of a zonula occludens (o) with on the A fracture face about seven horizontal ridges, which seal the cochlear d ct (CD) Th A fracture faces (A) of the microvill show r many particles, whereas on the B fracture faces (B) only a few can be detected. × _5 000.
The arrowhead below right indicates direction of platinum shadowi g. The freeze-etch illustrations should be viewed from that direction
When unfi ed specimens are shown, this will be specified.

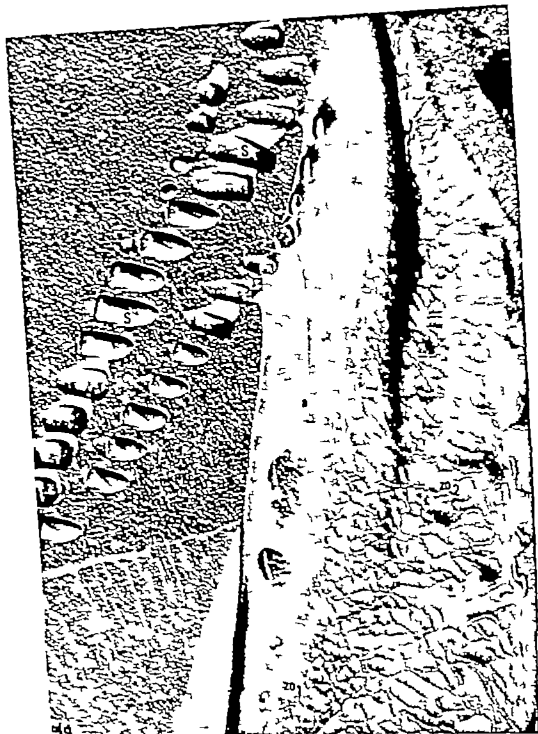


Fig. 4 Freeze etched organ of Corti, outer hair cell. On the right the very tight zonula occludens (zo) can be seen on the B fracture face. The total junctional depth is about 2.0 µm, and there are about 30 strands between the apical and the lateral membrane faces. T[illegible] regions of the zonula occludens can be distinguished (1) an apical region [illegible]th six to eight horizontally running strands and (2) [illegible] large distal zone, [illegible]hich consists of an irregular network of strands. The stereocilia (S) are obliquely fractured, with rather high particle density on their A fracture face and [illegible] few particles only on their B fracture face. The same is true for the apical membrane face ( ) of the hair cells. dm = upper part of the system of discontinuous membranes. [illegible] 30,000.

fracture of most zonulae occludentes which seal the cochlear duct reveals a band of five to eight interconnecting ridges on the A fracture face and complementary interconnecting grooves on the B fracture face (fig. 1 2, 3 15) This is consistent with the "intermediate to tight" type of zonula occludens (Claude and Goodenough 1973) An important exception is the "very tight" zonula occludens of the reticular lamina in the organ of Corti (see below) Where three cells join the zonula occludens extends basally along the facing lateral cell membranes. There one can observe up to twelve or more strands, of which the lower ones are very short (fig. 15) Some isolated strands are visible basally to the zonulae occludentes. The thickness of the ridges is about 90 Å. Particularly in the region distal to the zonula occludens, single particles can be found (fig. 15) Often in nonfixed specimens and sometimes in fixed specimens the ridges exhibit a particulate substructure and it may be that the particle-free intervals correspond to the particles which are seen in the B-face grooves (fig 4b)

The zonulae occludentes of the inner and outer hair cells and the supporting cells which are directly connected with them, are very tight (fig. 4a 4b 5) Two zones can be differentiated There is an apical band which has rather parallel strands, six to eight in number and which is similar to the intermediate to tight zonulae occludentes described above The large distal zone consists of irregular strands which form polygonal fields of very different sizes. In total one can count up to 30 strands or more which form junctions of about 2 μ width On the B fracture face grooves many particles of different size are observed whereas in the polygonal fields there are only a few particles (4b)

Two distinct membrane appearences of the stereocilia are produced by the fracture process, a concave A fracture face and a convex B fracture face While one can see a moderate number of diffuse particles on the A fracture face of both the stereocilia membranes and the apical cell membranes, relatively few particles are found on the B fracture face An interesting finding are the A and the B fracture face particles around the base of the stereocilia (fig. 5) In cross fractured stereocilia a fibrillar substructure can be indentified, with a diameter of about 100 Å (fig. 5)

Freeze-etch replicas of the outer and inner hair cells gave additional information concerning the discontinuous membranes These membrane systems are parallel to the lateral cell membranes and show only some particles when freeze fractured which are mostly clustered around the pores. Their pores are similar to the nuclear pores and are often arranged in circles. The diameter of the pores ranges from 800 to about 1000 Å (fig. 9) The discontinuous membranes have direct contact with the cuticular plate (fig. 4a)

Synaptic membranes also are split by the freeze-fracture procedure (Akert et al., 1972 Pfenninger et al., 1972) Thus in the synaptic regions of the inner and outer hair cells up to eight fracture faces can be observed these are the A and the B faces of the presynaptic as well as of the postsynaptic membrane at both the afferent and the efferent nerve terminals The exact definition of the synaptic membrane faces can be extremely difficult particularly when neither the nerve axoplasm nor the hair cell cytoplasm is cross-fractured and numerous replicas have to be evaluated.

Our preliminary observations of the hair cell synaptic regions are as follows cross fractured hair cells have aspects analogous to ultrathin sections (fig. 6 7 8) At the site of afferent transmission some 500–800 Å vesicles can be observed in the cytoplasm. The structure of the subsurface cistern is similarly a single discontinuous membrane (fig. 7) While one can differentiate the vesicle-rich efferents from the afferents in cross fractured nerve terminals, it has not yet been possible to do so when the fracture plane runs in the axolemma. In the latter case the terminals exhibit relatively many A fracture face particles. To date the following structures can be defined on the synaptic membranes of the inner and outer hair cells On the A fracture faces homogenous particles are located in rows (fig. 8) and other homogenous particles are arranged in a thumb-print like scanning pattern, with a diameter of 80–90 Å (fig. 7 8) and a center-to-center distance of about 90 Å The distance between the latter rows is about 170 Å (fig. 7) An



/ 4 Fr -etched organ of Corti, oute hair cell. On the right the ry tight zonula occludens (zo) an be seen on the B fracture face. The total junctional depth is about 2.0 μm, and there are about 30 strands between the apical and the lateral membrane faces. Two regions of the zonula occludens can be distinguished (1) an apical region with six to eight horizontally running strands and (2) large distal zone, which consists of an irregular network of strands. The stereocilia (S) are obliquely fractured, with rather high particle density on their A fracture face and few particles only on their B fracture face. The same is true for he apical membrane face (a) of the hair cells du = upper part of the system of discontinuous membranes 30 000.

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Synaptic membranes also are split by the freeze-fracture procedure (Akert et al., 1972 Pfenninger et al., 1972) Thus in the synaptic regions of the inner and outer hair cells up to eight fracture faces *can be observed; these are the A and the B faces* of the presynaptic as well as of the postsynaptic membrane at both the afferent and the efferent nerve terminals. The exact definition of the synaptic membrane faces can be extremely difficult particularly when neither the nerve axoplasm nor the hair cell cytoplasm is cross fractured and numerous replicas have to be evaluated.

Our preliminary observations of the *hair cell synaptic regions* are as follows cross fractured hair cells have aspects analogous to ultrathin sections (fig. 6 7 8) At the site of afferent transmission some *500–800 Å vesicles can be observed in* the cytoplasm The structure of the subsurface *cistern is similarly a single* discontinuous membrane (fig. 7) While one can differentiate the vesicle rich efferents from the afferents in cross-fractured nerve terminals, it *has not yet* been possible to do so when the fracture plane runs in the axolemma. In the latter case the terminals exhibit relatively many A fracture face particles. To date the following structures can be defined on the synaptic membranes of the inner and outer hair cells On the A fracture faces *homogenous particles are located in* rows (fig. 8) and other homogenous particles are *arranged in a thumb-print-like scanning pattern* with a diameter of 80–90 Å (fig. 7 8) and a center to-center distance of about 90 Å. The distance between the latter rows is about 170 Å (fig. 7) An

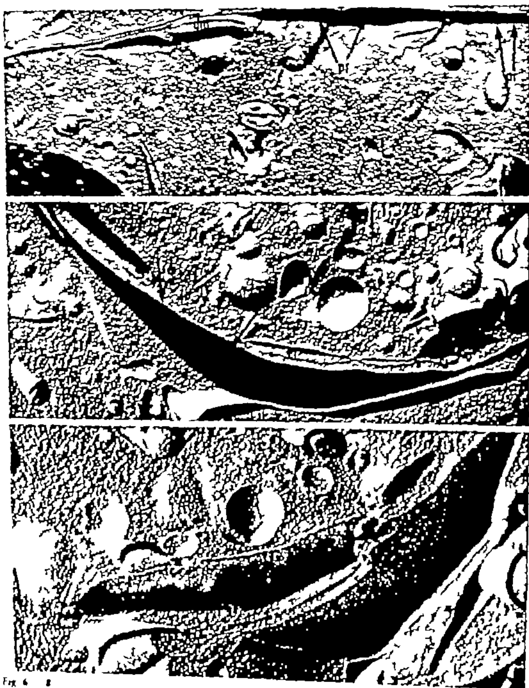


Fig. 6 – 8

Freeze-etched organ of Corti, synaptic regions of inner hair cells.

Fig. 6 The B fracture face of an inner hair cell membrane reveals small protuberances (pr.) In the cytoplasm are many small vesicles (v). Below left is the A fracture face of the outer nuclear membrane (nm) with some pores. dm = discontinuous membrane × 20 000.

Fig. 7 The A fracture face of an inner hair cell membrane, which shows "thumb-print-like" particle pattern (arrow). There are about 60 rows of particles, with diameter of 80–90 Å and a center to center distance of about 90 Å. The distance between the rows is about 170 Å. In the hair cell cytoplasm subsynaptic cistern (cl) is cross- and tangentially fractured. v = vesicles. × 35.000.

Fig. 8 The hair cell membrane has been cross-fractured and on the left ...

4b   5

ig. 4b H gher magnification of the outer hair cell zonula oc l dens of fig. 4a. On the lower left the relati ely th n pical region (1) The rest of the figure is occupied by the irregular polygonal fields of the large distal region (2) ome particles are associated with grooves on the B fracture face. × 90.000.

g 5 Freeze-etched organ of Corti, nner hai cell. The typical features of a zonula occludens (zo) of the cochlear nsory epithel um are visible in the upper part of the picture Some cross-f actured fibril (f) nside the stereocilia can be seen on the B fracture face of the pical ha cell membrane The diameters of the stereocilia are ery ari- le Only a few particles are observed, which are often situated nea the base of the stereocilia CD = cochlea ct cu = cuticula plate mv = microvill of a neighbouring ph:



Fig. 11 Freeze-etched tympanic covering layer. Both A and B fracture faces of nexuses or gap junctions (nA, nB) on the mesothelial cells can be observed, although their occurrence is rather rare. The general particle density of the A fracture faces (pA) is much higher than that of the B fracture faces (pB). × 50 000.

other peculiar feature of the hair cell A fracture face is the presence of small depressions. They are complementary to small protuberances on the B fracture faces of the hair cell membrane resembling the protuberances on presynaptic membranes in the central nervous system (Pfenninger et al., 1972).

The nexus (Dewey and Barr 1964) or *gap junction* is probably the type of cell junction responsible for direct electrical and metabolic coupling providing cell-to-cell transfer of ions and cellular metabolites (see Bennett, 1973). In freeze-fracturing the split membranes at the nexus exhibit either arrays of particles about 80 Å in diameter on the A fracture face or complementary arrays of small pits or depressions on the B fracture face. Usually the arrays are hexagonal with 90 to 100 Å center-to-center-spacing (Kreutziger 1968, Chalcroft and Bullivant, 1970). In the spiral ligament many gap junctions are seen on the fibrocytes (fig. 12, 13). They have various sizes and appear to interconnect all cells of the spiral ligament. Such intercellular junctions are also detected between these fibrocytes and the basal cells of the stria vascularis, as was previously reported (Jahnke, 1974, 1975). The A fracture faces of the fibrocytes are very particle-rich (fig. 12, 13). By thorough examination one can recognize particles of various sizes (fig. 12, 13). Where the cytoplasm is cross-fractured, fibrils or bundles of fibrils can be distinguished in fairly regular orientation (fig. 13). Scala vestibuli (fig. 11) and scala tympani are lined by some layers of flat mesothelial cells, which are not a true diffusion barrier.

Only a few gap junctions can be observed on the cells of the tympanic covering layer (fig. 11) while there are particle aggregations which are usually interpreted as cross-fractured desmosomal cell contacts (fig. 10).

The nonsensory cells lining the cochlear duct are joined by a few gap junctions, e.g. the epithelial cells of the outer sulcus (fig. 14). The most important finding is that all supporting cells of the organ of Corti are coupled by gap junctions (fig. 15, 16, 18, 19). The size of the nexuses in the organ of Corti is very variable. Generally larger gap junctions are found in the distal supporting cell regions. On the other hand our illustrations show examples of medium to large gap junctions in the upper part of the cells (fig. 15, 16) and rather small *gap junctions basally* (fig. 18). Sometimes one may get the impression, that the nexus subunit on *A fracture face* has a *central depression* corresponding to the proposed hydrophilic intercytoplasmic channel (fig. 19), but it cannot ruled out to be a preparation artifact.

Rectangular arrays of small membrane associated particles 60 to 70 Å diameter is a characteristic and common finding in apical regions of the supporting cells in the organ of Corti as demonstrated in figure 15.

Freeze-fracturing of the inner and outer pillar cytoplasm reveals the fine structure and three-

Fig 9 Freeze-etched organ of Corti outer ha cell (OHC) The fractured d scontinuous membranes (dm) exhibit pores (po) arranged i ci cles. Th diameter of the pores is about 800 to 1000 Å. In the pore-regions the discontinu ous membranes contain many particles. ICS = intercellula space. × 30.000.

Fig 10 Freeze-etched tympanic co ering layer Small particle aggregations (d) representing desmosomal contacts, can be seen on the A fracture faces of the mesothelial cells. Many organelles are observed in the cytopl m (cy) e.g. a tangentially fractured mitochondrium (m) which shows different faces of its nner nd uter membranes. × 30,000



Fig. 1[illegible] [illegible] organ of Corti, apical region of Hensen cells (HeC). The replica exposes both A and B fracture faces of [illegible] membranes. [illegible] Below one sees [illegible] zonula occludens (zo) with about eight horizontal strands and some additional short strands in the [illegible] area [illegible] where three cells are in contact (arrow). In the distal fields of the zonula occludens single particles (p) are present. The A and B fracture faces of the microvilli (mv) are particle-rich. CD = cochlear duct.



Fig. 1 Freeze-etched spiral ligament. This shows the almost complete *A fracture face of a macular nexus (nA)* and many particles (pA) on the A fracture face of a fibrocyte. Also shown are the flat mesothelial cells (M) which line *the scala vestibuli (SV)* × 45 000

Fig. 13 Freeze-etched spiral ligament. Large areas of the particle-rich A fracture face (A) and some particles on the B fracture face (B) of fibrocyte cell membranes are exposed in this replica. The cleavage plane has revealed two faces at the site of the nexuses. Face A (nA) is covered with closely packed particles and face B (nB) exhibits a complementary array of small pits. The cross-fractured cytoplasm shows fibrils (f) × 45 000

Fig. 14 Freeze-etched outer sulcus. A macula nexus (n) connects the epithelial cells (FC) which line the outer sulcus. *Here the zonula occludens (zo) is obliquely fractured.* m = microvilli, CD = cochlear duct × 40 000.

Fig. 15 Freeze-etched organ of Corti. Hensen cell. To the left a gap junction (n) with relatively widely spaced particles. There are some rectangular arrays of membrane-associated particles (ra) on the A fracture face of the Hensen cell × 5 000



Fig. 16. [illegible] organ of Corti, apical region of Hensen cells (HeC). The replica exposes both A and B fracture faces of [illegible]. Below one sees zonula occludens (zo) with about eight horizontal strands and some additional short strands in the area, where three cells are in contact (arrow). In the distal fields of the zonula occludens single particles (p) are present. The A and B fracture faces of the microvilli (mv) are particle-rich. CD = cochlear duct [illegible] 49,000.





Fig. 12. Freeze-etched spiral ligament. This shows the almost complete A fracture face of a macular nexus (nA) and many particles (pA) on the A fracture face of a fibrocyte. Also shown are the flat mesothelial cells (M) which line the scala vestib l (SV) × 45 000

Fig. 13 Freeze-et hed p ral ligament Large areas of the particle-rich A fracture face (A) and some particles on the B fracture fa e (B) of fibrocyte cell membranes are xposed thu replica. The cleavage plane has revealed two faces at the site of th nexuses face A (nA) is covered with closely packed particles and face B (nB) exhibits a complementary array of small p ts. The ross fr tured cytoplasm shows fibrils (f) × 45 000

F g 14 Freeze-etched out r sulcus. A macular ne us (n) onnects th epithelial cell (EC) which line the o t r sul us. Here the zonula occluden (zo) is obliquely f tured. m = m cro ll CD = cochlea duct × 40,000.

Fig. 15 Freeze-et hed organ of Corti Hensen ell. To the left is a gap junction (n) with relati ely widely spaced parti les. There re some rectang la arr y of membrane sociated particles (ra) on the A fracture face of the Hensen cell. × 5 000

Fig. 19. Freeze-etched organ of Corti, higher magnification of nuclear membranes of outer phalangeal (Deiters') cells. The polygonal packing of the A (nA) and B (nB) fracture face components is particularly striking. × 100,000.

Fig. 20. Freeze-etched stria vascularis vessel. *Freeze-fracturing* reveals the A fracture face of the luminal plasma membrane of the endothelial cell. Region of *tight junction (tj). The membrane is very particle-rich.* Some micropinocytotic vesicles (mp) are observed as invaginations on the *A fracture face.* The contact between the vessel and the *basal cells* (BC) appears to be close. [illegible] × 36,000.

F g 17 *Freeze-et hed organ of Corti tangentially fractured out r pilla cell (OPC) The replica show the* pattern of tubuli (t) w th central pores. The outer diameter of each tubulus is about 260 Å ICS = inter cellula pace. × 25 000

Fig 18 Freez -etched organ of Corti, inner pilla cell. Some nexuses ( ) of different sizes can be seen i the *basal region of the cell. Where th cytopla m i cross-fract red, some tubuli (t) are vi ible ICS = inter* cell lar space. × 30 000



Fig. 2. Stria vascularis lateral region, in freeze-etch replica of unfixed tissue. On the upper right some tangentially fractured basal cells exhibit tight junctions. They often have [illegible] short parallel strands (arrows). The A fracture faces of the basal cells contain some particles (pBC), whereas the A fracture faces of the marginal cell extensions have numerous particles (pMC). m = cross-fractured mitochondria.



Fig. 21 Freeze-etched stria vascularis, lateral region. The fracture face reveals an extensive ramifying tight junction of the basal cells. The strands are arranged in a network, with rows of particles on the B fracture face (tB) and some particles on the A fracture face (tA). The latter are associated with complementary slight elevations of the membrane. In the upper part of the picture several rather large nexuses can be observed as closely packed particles on the A fracture face (nA) and as complementary arrays of pits on the B fracture face (nB). MC = marginal cell extension with mitochondria, cy = cytoplasm of a basal cell. × 25 000.



Fig. 22 Stria vascularis lateral region, in freeze-etch replica of unfixed tissue. On the upper right some tangentially fractured basal cells exhibit tight junctions. They often have two short parallel strands (arrows). The A fracture faces of the basal cells contain some particles (pBC) whereas the A fracture faces of the marginal cell extensions have numerous particles (pMC). m = cross-fractured mitochondria. 40,000.



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23

Fig. 23 The perilymph-endolymph-barrier of the cochlea and the stria vascularis. This diagram summarizes the results of observations on tight junctions, which seal the cochlear duct and the intercellular spaces of the stria vascularis. SV = scala vestibuli, ST = scala tympani, CD = cochlear duct, OC = organ of Corti, S = stria vascularis, SL = spiral ligament. All nonsensory epithelia, which line the cochlear duct, have zonulae occludentes of the intermediate to tight type (dotted line). In contrast, the zonulae occludentes of the cochlear sensory epithelium as well as the tight junctions of basal cells of the stria vascularis are very tight (thick black line). The circles represent blood vessels, which all have tight junctions, such that their nonfenestrated endothelia also form barriers.

Angelborg, 1974) and horseradish peroxidase (Duvall and Sutherland, 1977; Masuda, 1972; Jahnke, 1972 and 1973). Thus it is not surprising that the zonulae occludentes of the nonsensory epithelium of the organ of Corti, such as the Hensen cells are very similar to those of other epithelial cells lining the cochlear duct. We also believe that they maintain the same resting potential difference as the other epithelial cells of the perilymph-endolymph-barrier (see below). The "very tight" zonulae occludentes of the cochlear sensory epithelia are also components of the perilymph-endolymph-barrier. In addition, the numerous strands can be explained by the function of the hair cell as mechanoreceptors. *It is essential that these sensory cells are anchored very firmly in order that disturbance by movements of small molecules can be prevented and that they have resistance to powerful forces which follow acoustic noises.*

The fine structure of tight junctions may be changed in some inner ear diseases. Recently Wade and Karnovsky (1974b) demonstrated osmotic

dimensional arrangement of their tubuli (fig. 17 18) Their total diameter is about 260 Å and that of the lumen about 100 Å

In freeze-fracturing one gains additional information concerning *the particle densities* of the apical epithelial cell membranes which line the cochlear duct (fig. 1–3 14 16) and particularly the membranes of the microvilli Generally their convex A fracture faces have a medium to high particle density especially in the marginal cells of the stria vascularis the spiral prominence epithelium and some outer sulcus epithelia and the Hensen cells.

The *spiral vessel the vessels of the spiral ligament the spiral limbus and the stria vascularis* are nonfenestrated. Their endothelial cells are connected by tight junctions. In freeze-fracture replicas these tight junctions consist of very differing numbers of strands in the same region. The arrangement of the strands and their substructures have a closer resemblance to the strands of the basal cells of the stria vascularis than they have to epithelial cells. Of special interest is the presence of a particulate substructure in the tight junctions of the vessels. Other features of freeze fractured vessels are very high particle densities particularly in the vessels of the stria vascularis and a varying frequency of micropinocytotic vesicles The latter are mostly seen as invaginations on the A fracture face (fig. 20) and as protrusions on the B fracture face. In some capillaries of the stria vascularis and of the spiral prominence nexuses were present connecting endothelial cells

In order to give a more complete picture of the tissues which surround the cochlear duct the freeze-fractured fine structure of the *stria vascularis* will be briefly summarized Whereas the marginal cells and their intermediate to tight zonulae occludentes represent the barrier between the endolymphatic space and the stria vascularis intercellular spaces, the latter are sealed to the spiral ligament by the "very tight tight junctions of the basal cells (fig. 21 22) Thus it is confirmed that the intercellular spaces of the stria vascularis are a compartment. The tight junctions of the basal cells exhibit a network of strands, and a particulate substructure – on the B fracture face – is noted more often than in the epithelial tight junctions. Thin tenuous grooves associated with slight membrane elevations (fig. 21) can be observed on the A fracture faces. Within these areas gap junctions are often seen Of special importance is the finding that all stria vascularis cells are coupled by gap junctions. Another notable feature is that the marginal cell membranes particularly the membranes of their extensions are extremely particle rich (fig 22) a sign of very high metabolic activity

B DISCUSSION

The results of our observations on the perilymph endolymph-barrier of the cochlea as well as the compartment of the *intercellular spaces of the stria vascularis* are summarized in figure 23 In general the zonulae occludentes of the nonsensory epithelia which seal the cochlear duct consist of approximately four to eight horizontal strands. According to the report by Claude and Goodenough (1973) this is the "intermediate to tight"-type of zonula occludens. These authors compared electrophysiological and fine structural observations with respect to the transepithelial permeability They found that junctions of "tight epithelia show five or more strands, whereas in leaky epithelia" only a few strands are present Their findings agree with the results of Friend and Gilula (1972) and other authors. It is well known that in regions where three epithelial cells are in contact the zonula occludens extends basally and shows more strands (see Staehelin, 1973) Our findings indicate that epithelia with zonulae occludentes which consist of four to eight strands, are able to maintain the resting potential difference of about 90 mV between the cochlear duct and the perilymphatic spaces. The same is true for the marked electrolyte concentration gradients between the potassium-rich endolymph and the sodium-rich perilymph It must be pointed out that *active membrane processes* also play an essential role.

Tasaki et al. (1954) postulated that the electrolyte concentrations of the intercellular fluid of the organ of Corti ("cortilymph") are similar to those of the perilymph. This has been supported by several tracer studies with thorotrast (von Ilberg, 1968b;

particle rows of the nerve terminal membranes of motor endplates which may be associated with synaptic vesicle fusion and transmitter release (Dreyer et al., 1973 Rash and Ellisman, 1974)

Electrotonic coupling is characterized by a low end resistance to the intercellular passage of ions. Nexuses are the cell junctions which are thought to provide cell-to-cell transfer of ions by means of their intercytoplasmic channels (see McNutt and Weinstein, 1973 Bennett, 1973) Such transfer is presumably also possible for cellular metabolites (Gilula et al., 1972). The closely packed globular particles on the A fracture face are interpreted as the morphological correlates of the hydrophilic channels.

In the present study it was demonstrated that coupling of cells by nexuses is a very common feature of cochlear tissue. In this respect the most important finding is perhaps that nexuses connect all supporting cells of the organ of Corti. There is negative resting potential of about 70 mV and it is still uncertain whether it was measured intracellularly or extracellularly (see Dallos, 1973) One of the arguments against the first suggestion is that it is technically difficult to obtain pure intracellular readings. However our results which indicate that there is electrotonic coupling of all supporting cells in the organ of Corti by nexuses, are t variance and suggest that it is possible t measure the resting potential intracellularly It has been previously reported and discussed in detail (Jahnke 1975) that all cells of the stria vascularis are coupled by nexuses. In this connection it is of interest that the spiral ligament fibrocytes are also coupled with the basal cells of the stria ascularis by such junctions. One prerequisite for the formation of nexuses between the basal cells and the fibrocytes may be that the stria vascularis cells lack a basement membrane.

The rectangular arrays of particles which occur on plasma membranes of the supporting cells of the inner ear sensory epithelia will be discussed in part IV

The endothelial cells of the inner ear capillaries represent the site of the blood-perilymph-barrier except for some fenestrated capillaries of the cochlear plexus. Tight junctions are located between the plasma membranes of these endothelial cells, and they are impermeable to tracers such a horseradish peroxidase (Jahnke and Gorgas, 1974) Now freeze-fracture replicas of inner ear capillaries have revealed the fine structure of the tight junctions. Since they are composed of single particles they are more similar to the network-like tight junctions of the basal cells of the stria vascularis (Jahnke, 1975) than to the zonulae occludentes of the epithelial cells of the cochlear duct. That is a one could expect because both the capillary endothelial cells and the basal cells re of mesenchymal origin. In the regenerating rat liver Yee and Revel (1975) observed similar particles *in regions of* contact between endothelial cells lining the hepatic sinusoids. The number of strands can be ery ariable, and one can gain the impression of rather "leaky" and of "tight" type functional regions next to each other

IV The vestibular sensory epithelia

A OBSERVATIONS

The freeze fracture observations on the maculae sacculi et utriculi and on the cristae ampullares will be described together because the results agree in all essential points.

The *zonulae occludentes* of the vestibular nonsensory regions are of the "intermediate to tight" type (fig. 29), whereas all vestibular sensory epithelia are sealed by zonulae occludentes of the "very tight" type (fig. 24, 25a 27 28, 35a) Here one can also distinguish a small apical zone with more *parallel strands and a* large distal zone with a net work of strands. It should be pointed out that the strands are less frequent than in the organ of Corti. Especially the distal network is looser and single strands can be seen more often (fig. 25a, 29)

The stereocilia of the vestibular hair cells show

disruptions of single strands of the zonulae occludentes in the toad urinary bladder which are reversible. In the pathogenesis of Menière's disease *alterations of the osmotic pressure of the endolymph* are thought to be an essential step. These could produce *disruptions of single strands of the zonulae occludentes* which seal the endolymphatic space. The zonulae occludentes would become "leaky" and the following ion concentration changes would lead to a decrease of the microphonics. In our opinion this may explain the hearing fluctuations which occur in patients with Menière's disease Acute acoustic trauma also may cause disruptions of single zonula occludens strands.

Intramembranous particles represent the protein component of membranes (see Bretscher 1973) Their higher frequency on the A fracture faces of the membranes is due to the fact that the membranes are asymmetrical and contain more protein in their cytoplasm adjacent layer The particles on the B fracture face are thought to be proteins or parts of proteins which extend from one cell membrane surface to the other Such particles *appear to be involved in transport particularly of* small molecules, e.g ions, H_2O glucose (see Fox 1972) *and are called "carrier" proteins. In this* connection the particle pattern on the B fracture faces may be more interesting than on the A fracture faces But it cannot be ruled out that some of the A fracture face particles are also carrier proteins.

The relatively few particles on the B fracture faces of the hair cell apical membranes and their stereocilia may explain the very high potential difference (> 150 mV) between the cochlear duct and the hair cells of the organ of Corti It may be important for mechano-electric *transduction that* there are some clusters of particles on the B frac*ture faces near the bases of the stereocilia.* It is suggested that the receptor potentials develop when the membrane resistence of the apical hair cell membrane has changed Flock (personal communication 1975) has shown in the lateral line organ of the burbot that the hairs of the sensory cells are stiff and that they are not bent but angled. This angulation may induce changes in ion-specific resistance in the apical hair cell membrane. The particles may be morphologically analogous to ion-channels, and their configurations could be altered in this way

The high particle densities of some apical nonsensory cell membranes lining the cochlear duct such as the marginal cells of the stria vascularis, are a sign *of high metabolic activity This is also a prominent* feature of the cell membranes of the marginal cell extensions, *as previously reported in detail* (Jahnke, 1975) This also applies to some vessel cell membranes, *particularly in the stria vascularis.* As yet the appearance of other particles seen in special regions such as in regions of the discontinuous membranes, cannot be interpreted. It should be noted however that they occur in fixed and in unfixed tissues.

The observations on the synaptic membrane faces are preliminary because only relatively few synaptic membranes can be viewed at an appropriate angle

The protuberances on the B fracture faces of the hair cells are presynaptic protuberances (see IV B) and are consistent with findings in the central nervous system *(Pfenninger et al 1972) These authors* have presented data that the protuberances are *temporary attachment* (or fusion) sites between synaptic vesicles and the presynaptic membrane and may be identical with the sites of transmitter release. A hexagonal arrangement of protuberances could not be demonstrated in this study At nerve terminals in the spinal cord the number of protuberances is decreased in anesthetized as compared with unanesthetized animals (Streit et al 1972) We do not suppose that the fine structure of presynaptic membranes at *the synapses of the* inner ear is changed to such an extent in anesthe*tized guinea pigs. The* special thumbprint like particle pattern on the A fracture face of the hair cell synaptic membrane cannot be interpreted since only a few of such membranes have been clearly differentiated. The particles may be morphological equivalents of transmitter receptors or ion channels, – we do not know yet if this is a pre-synaptic or postsynaptic membrane *differentiation.* The two parallel rows of particles on the A fracture faces of the hair cells resemble the similar

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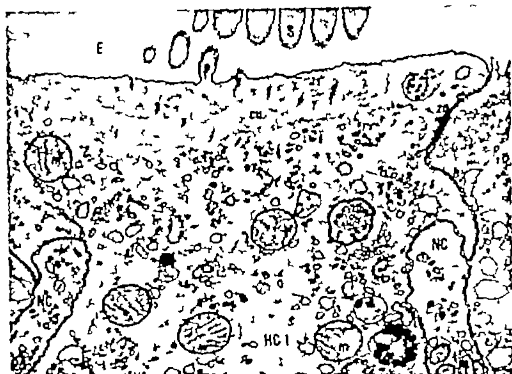


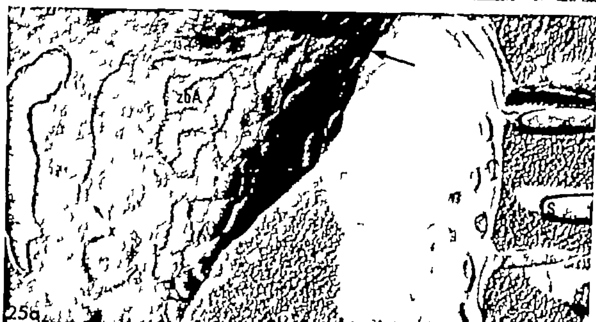
Fig. 26. Micrograph of thin-sectioned sensory epithelium of the crista ampullaris. The stereocilia (S) of the hair cell type I (HCI) are tangentially cut. One can see some of their roots (*r*) in the cuticular plate (cu). Several mitochondria (m) and many small vesicles occur in the cytoplasm of the hair cell and in the axoplasm of the nerve calyx (NC). On the upper right the zonula occludens (zo) seals the endolymphatic space (E). 25 000.

Fig. 24. Freeze-etched macula sacculi, apical hair cell region. The bases of cross-fractured stereocilia and some intact stereocilia (S) can be seen. Several particles (p) can be observed on the A fracture face of the apical hair cell membrane particularly near the bases of the stereocilia. mv = microvilli of neighbouring supporting cell, zo = zonula occludens (part). E = endolymphatic space. 35.000.

Fig. 25 a. Freeze-etched macula utriculi, apical hair cell type I region. The zonula occludens (zoA zoB) is of the ... tight type but its distal region is not as large as that of the hair cells of the organ of Corti. There are some isolated strands ( ). The arrow indicates an area where three cells are in contact. S = stereocilia. × 40.000.

Fig. 25 b. Stereocilia of the same hair cell. They show several particles on their A fracture faces (A) whereas only few particles can be detected on their B fracture faces (B). On the lower right is ... tangentially fractured kinocilium (arrows). On its A fracture face rows of small particles are present, called ciliary necklace. The between row distance is about 1 000 Å. 40.000


mv
p
p


zbA
S
25a


B
B

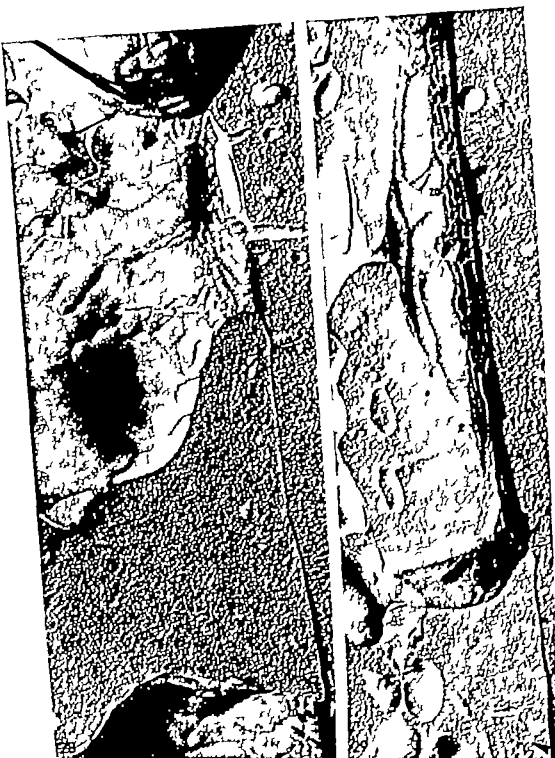
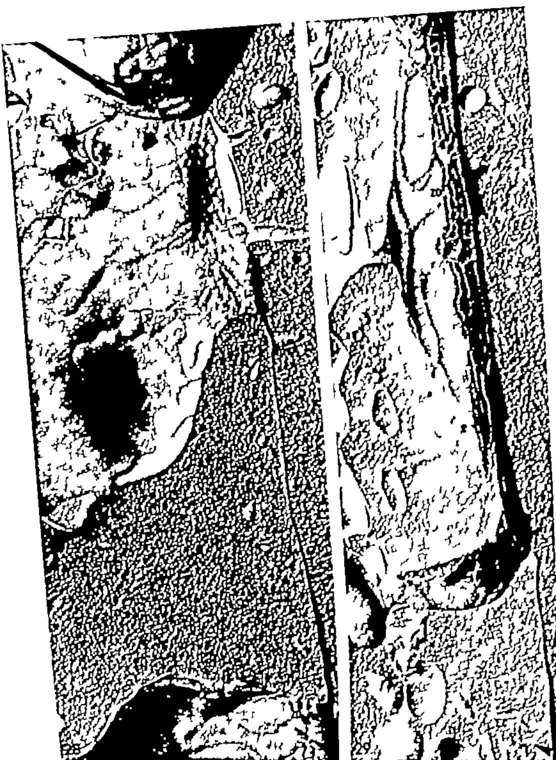




Fig 27 Freeze-etched crista ampullaris, sensory epithelium. The same region as shown in fig. 26, the hair cell type I *is almost completely detached. The replica exposes the characteristic features of a zonula occludens (zo) of the vestibular sensory epithelium* here seen on the B fracture face. Apically some small horizontal strands can be observed, whereas in the distal region there is an irregular network of strands. Some small protuberances are present on the B fracture face of the hair cell (pt) On the left the nerve calyx (NC) can be seen. E = endolymphatic space. × 35 000.

Fig 28 Freeze-et hed macula utriculi, periphery of the sensory epithel m. The zo ul occludens ( ) mainly be seen on the B fra ture face, w th narrow pical strands, whereas som strands extend basally along the f cing lateral cell memb anes Arrow indicates, where three cells re in contact. There are several particles on the *micro- illus A fracture f ce (mvA) and only a few on its* B fracture f ce (mvB) × 48 000

Fig 29 Free e-etched macula utriculi, transitional one. The zonula occludens (o) is mostly seen a a series of ridges on the A fracture face and i composed of at least si strands. × 40.000





F g 30 Freeze-etched macula sa cul sy ptic region of hair cell type I. The ha cell is mostly detached by the freeze fracturing. The view is taken from th position pre ously occupied by the hair cell. The replica reveals the B fracture f ce of the presynaptic ha cell type I membr ne (HCI) and the A fracture face of the postsynaptic nner ner calyx membrane (NC) The xoplasm of th nerve calyx (x) i cross-fractured. O the presynaptic B fracture f e two regions can be distingu hed (1) there are numerous large particles in one region where s ( ) in another region onl occasional small particles occur In both these reg ons small protuber nces (pt) re present The fra tur exposes n merous small particles and some small depression (de) on the A fracture face of the post synaptic membrane 5 000

a moderate number of diffuse membrane associated particles (fig. 24 25a, 25b) The convex A fracture face contains more particles than the concave B fracture face. On the ciliary membrane only a few diffuse particles can be observed. On the A fracture face of the distal *kinocilium* region, 90 Å particles are arranged around the kinocilium in circles which are bout 800-1000 Å apart (fig. 25b) This membrane differentiation is called the ciliary necklace (Gilula and Satir 1972) I the vestibular sensory epithelia particles are also ggregated around the stereocilia bases (fig. 24)

In the vestibular sensory epithelia of mammals and birds two types of hair cells are found. Hair cells of type I are surrounded by a large afferent nerve calyx, enclosing the major p rt of the flask shaped cell, whereas efferent terminals contact the afferent nerve fibers or the nerve calyx. The hair cells of type II are more oblong, and they are inner ated by mall afferent and efferent nerve terminals on the basal part of each cell (Wersäll, 1956 see Engstrom et al., 1974) On the bottom of both hair cell types synaptic modifications are observed which suggest that there is chemical mode of synaptic transmission. However areas of very close appositions between the nerv calyx and the hair cell type I on its basal part can be seen in thin sections. The possibility of electrical synaptic transmission has been discussed by many authors (see Hamilton, 1968).

As in the organ of Corti, eight different fractur faces (Akert et al. 1972) can also be seen in the *vestibular synaptic regions*. Since the hair cell type I is mainly surrounded by an afferent nerve calyx, only four different f acture faces occur in that contact region. The split synaptic hair cell type I membrane represents the presynaptic A and B fracture faces. On its B fracture face areas with high density of large homogeneous particles can be dif ferentiated from egions with only a few small particles (fig. 30 31 and b) The large particles ha a diameter of about 130 Å. In both regions many small protuberances (fig. 30, 31 a and b) are present which resemble the protuberances of the central nervous system ynapses (Pfenninger et al., 1972) Some of these structures usually can also be seen in the upper synaptic zone of the hair cell type I (fig. 27) as well as on the presynaptic B fracture faces of the hair cell type II membrane (fig. 3) Complementary small depressions or pits can be detected on the A fracture faces of the ha r cells. On the A fracture face of the postsynaptic nerve calyx membrane a very high density of homogeneous particles is observed. Some small depressions also occur

Other membrane features of the estibular synaptic regions are similar to those in the organ of Corti, e.g. rows of particles on the A fracture face of hair cell type II and particles on the A-fracture faces of nerv terminals. Membrane features which could be interpreted as sites of electrical transmission, have not been found in this material.

All nonsensory epithelial cells of the vestibular apparatus are coupled by *nexuses* e.g. the *supporting cells of the cristae ampullares* (fig. 33) Below the ery tight zonulae occludentes of the sensory epithelia large gap junctions are situated between tight junction strands which extend basally (fig. 34a, b c) Many small *rectangular arrays* of membrane-associated particles with a diameter of 60 to 70 Å can be seen on the A fracture face of those supporting cells which are adjacent to the nerve calyx (fig. 34a, b, c) They are often composed of only few subunits.

Directly below the zonulae occludentes of *nonsensory* estibular epithelia particle aggregations are present which are considered to be desmosomal contacts.

Freeze-fracture replicas of *vestibular subepithelial vessels* reveal structures similar to those described in the cochlear vessels. The tight junctions consist of *ery differing numbers* of strands in the same region. Their appearance is illustrated by figures 36a and 36b. In unfixed specimen the particle substructure of the strands is clearly visible.

B DISCUSSION

Many fine structure observations on the freeze fractured membranes of the vestibular apparatus are analogous to those on the membranes of the cochlea which have been discussed above. The zonulae occludentes of all vestibular nonsensory *epithelia* which seal the endolymphatic space con

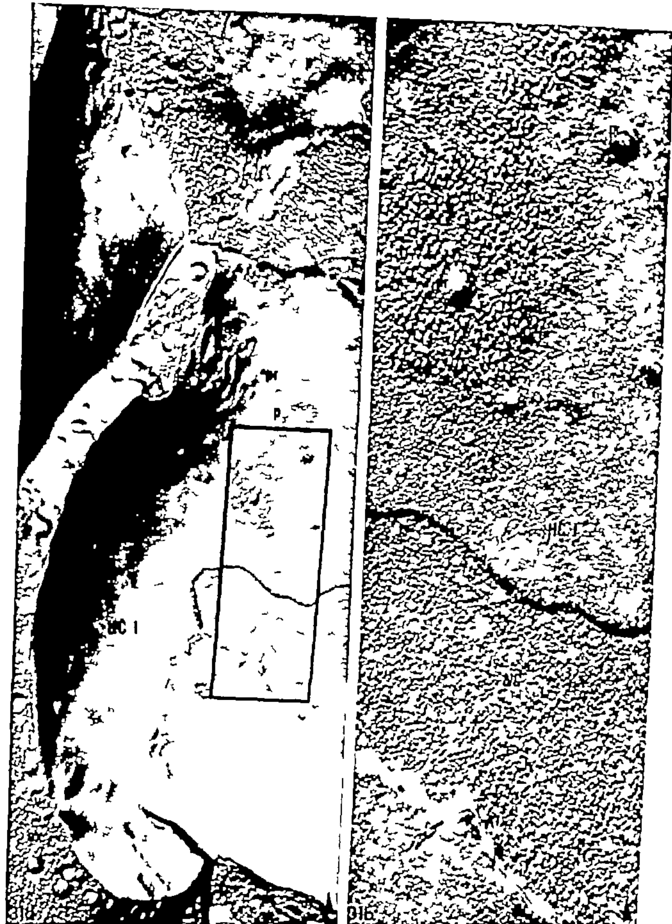


Fig. 31a Freeze-etched crista ampullaris, synaptic region of a hair cell type I. The fracture reveals the B fracture face of the presynaptic hair cell membrane (HCI) with clusters of large particles (p) and small protuberances (pr). On the left the axoplasm of the nerve calyx (a) which contains some vesicles ( ) is cross-fractured. × 36 000



Fig. 32 Freeze-etched crista ampullaris, basal region of hair cell type II. On the lower left cross-fractured nerve terminal (N) can be seen, with small vesicles ( ) and cross-fractured mitochondrium (m) in its axoplasm. The B fracture face of the hair cell membrane, which is probably presynaptic show small protuberances (small arrows). On the right nodular membrane features are observed. The hair cell cytoplasm also contains several small vesicles (v). The inner A (nuA) and outer B (nuB) faces of the nuclear membranes with cross-fractured pores are visible. On the upper right one can detect the transition (arrow) of the nuclear membrane to the endoplasmic reticulum (eR). SC = supporting cell. 25.000.

Fig. 33 Freeze-etched crista ampullaris, supporting cell of the sensory epithelium. Several gap junctions (nB) of various sizes can be seen on the B fracture of the middle region of the cell. In the center of the picture an isolated struc (dB) is present. 50 000.

Fig. 31b Higher magnification of framed area in fig. 31. The upper region of the picture demonstrates the presynaptic B fracture face (HCI) with clusters of larger particles (*p*) with diameter of about 130 Å as well as small crater-like protuberances (pr). Below the A fracture face of the postsynaptic membrane (NC) show diffuse small particles with diameter of about 90 Å. 90.000.

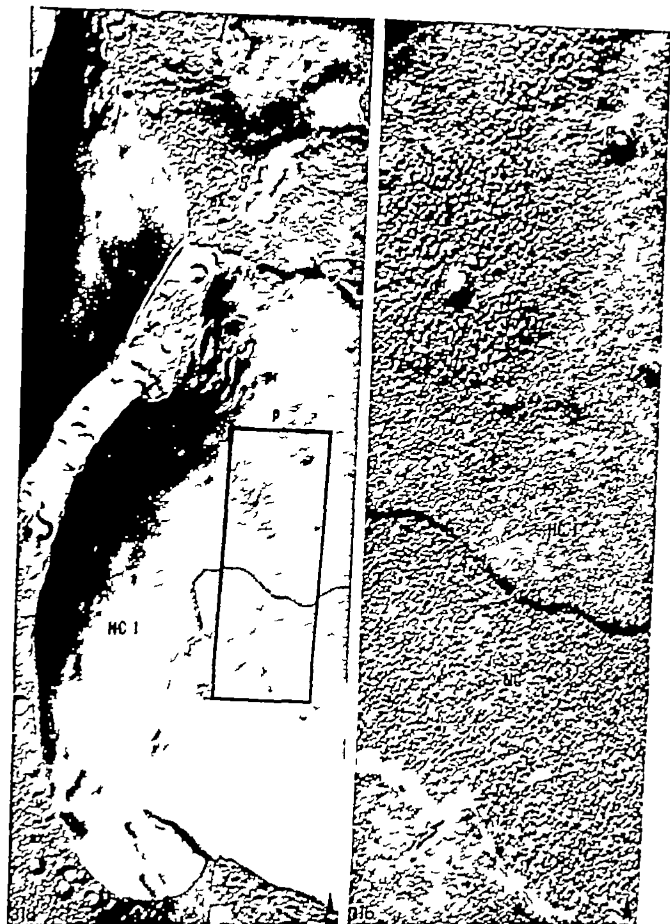


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Fig 34 Freeze-etched macula sacculi, subepithelial tissue. The fibrocytes of this region are also connected by gap junctions (nA nB) as illustrated by this figure. There is a high particle density (p) on the A fracture face of the fibrocytes. × 48 000.

sist of a similar fine structure as those of the coch lear nonsensory epithelia. They are of the "inter mediate to tight type, whereas zonulae occludentes of the very tight type can be found in the vestibular *sensory epithelia* The latter are com posed of a lower number of strands than those in the organ of Corti. In both sensory areas similar ion concentration gradients have been measured but the difference in the resting potential between the endolymphatic space and the surrounding perilymphatic spaces is much *higher* in the coch lea than it is in the vestibular labyrinth. Johnstone and Sellick (1973) recorded + 70 to 90 mV in the cochlea, − 8 to + 2 mV in the saccule and − 3 to + 5 mV in the utricle. In addition these authors concluded from their experiments that the utricular endolymph and potential is independent from the cochlea but the saccule derives its potential and endolymph from the scala media via the ductus reuniens The very tight zonulae occludentes are thought to be an essential stability factor for the function of the hair cells as mechanoreceptors.

The remarkable particle aggregations around the bases of the stereocilia could also be observed in the apical cell membranes of the vestibular hair cells It is possible that these particles are morphological equivalents of ionic permeability sites and that they mediate the first step of the mechanoelectric transduction mechanism

Every vestibular hair cell shows one kinocilium on its apical membrane. The fracture faces of the kinocilium membrane contain only a few particles compared with those of the stereocilia However there are particle rows which surround the lower region of the kinocilium membrane just above its junction with the apical cell membrane. This longitudinal arrangement of particles has been de scribed earlier on the A fracture faces of kinocilia in many nonsensory epithelia and has been termed the ciliary necklace which may be involved in energy transduction (Gilula and Satir 1972) The kinocilia of the vestibular sensory epithelia contain a higher number of strands than most of the kinocilia, which were described by these authors, and

Fig 35a b and c

Freeze-etched crista ampullaris, apical regio of th sensory ep thelium. A hair cell type I and its nerve calyx are detached by freeze fracturing.

Fig 35a Zonulae occludentes (o) wh ch seal the endolymphatic space (E) can be seen. The fracture process has revealed nexuses (n) f ariou zes, wh ch presumably connect the supporting cell in this region. They are located between basally extending trand ( ) of the zonulae occl dentes. × 15 000.

Fig 35b The nexuses (nA B) a d the strands (s) are shown at higher magnification. The strands on the A fracture face consist of particles *irregular rows*. On the A fracture face of the upporting cell recta gula rr ys (ra) of small particles can be observed. × 50 000

Fig 35c. The rectangular arrays (ra) are composed of closely packed particles which have a diameter of 60–70 Å. n = nexus, s = strands. × 100 000

the distance of the single strands is also higher in our material.

All nonsensory epithelial cells of the vestibular labyrinth seem to be electrotonically coupled by nexuses, as it has been shown for the epithelial cells lining the cochlear duct.

Another membrane speciality which also has been found in the organ of Corti, is the rectangular array and this is very common finding in the vestibular sensory epithelia. Staehelin (1973) described rectangular arrays of A fracture face particles with a center-to-center spacing of approximately 70 Å and complementary pits on the B fracture faces of rat intestinal epithelial cells. These structures were termed "type III" gap junctions. Later on similar rectangular arrays of small particles were observed on the fracture faces of the sarcolemmas of adult rat diaphragm myofibers (Rash et al., 1974). Since these myofibers are separated by basement membranes and are not electrotonically coupled it was concluded that the rectangular arrays of small particles cannot be the morphological or functional equivalents of gap junctions. Similar arrays were observed on freeze-fractured astrocytes (Landis and Reese, 1974), and light cells of the kidney collecting tubule (Humbert et al., 1975). At present, no function is known for the rectangular arrays of small particles. In the astrocytes they have been attributed a possible role in the permeability of the cell membrane (Landis and Reese, 1974). This might be true for the rectangular arrays of supporting cells in both the cochlear and vestibular sensory epithelia. Up to now it cannot be decided, if all supporting cells of the inner ear sensory epithelia are provided with such particle arrays which could be demonstrated in the supranuclear regions of the cells.

Many findings in the vestibular synaptic regions were similar to those in the cochlea which have been described and discussed in part III. A special advantage in the study of the vestibular labyrinth is that the hair cell type I-nerve calyx synapse is a synaptic contact of known identity which is thought to be afferent. The B fracture faces of the presynaptic hair cell type I membrane contain aggregations of large particles which we interprete as proteins involved in ion transport. Arrays of small protuberances on the presynaptic B fracture faces and complementary depressions on the A fracture faces have been described in the central nervous system (Akert et al., 1972; Pfenninger et al., 1972; Landis et al., 1974) and also in neuromuscular junctions (Dreyer et al., 1973; Rash and Ellisman, 1974). This prominent specialization of the presynaptic membrane presumably represents the fusion sites between synaptic vesicles and the hair cell membrane where the vesicles release their content of transmitter. Fracture faces of the postsynaptic nerve calyx membrane reveal a high number of particles. Such particles are interpreted as the sites of transmitter receptors, or they may be ion channels or enzymes which catalyze neurotransmitter degradation (Landis et al., 1974). However, it would be premature to discuss the functional significance of these findings in detail, because the chemical nature of the afferent inner ear transmitters is still unknown. At present, there is no evidence that electrical synapses also join the hair cell type I to the nerve calyx.

Application of the *freeze-fracture* technique to the study of vestibular subepithelial blood vessels confirms our findings in the cochlear vessels. The described structures represent the blood perilymph-barrier. They are of special pathophysiolo-

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Fig. 36 a. Blood vessel of the crista ampullaris, in freeze-etch replica of unfixed tissue. The fracture has exposed the A and B fracture faces of the endothelial cell membranes, the view is taken *from the* vessel lumen. The number of strands making up the tight junction ranges from three to twelve or more. Thin terminal grooves (tA) are seen on the A fracture face and rows of particles (tB) on the B fracture face. Micropinocytotic vesicles are observed as protrusions (mp). There are only a few particles on the endothelial cell membranes. cy = *cross-fractured* endothelial cell cytoplasm, F = fibrocyte. × 36,000

Fig. 36 b. The tight junction of the same vessel is seen on the B fracture face at higher magnification. Its fine structure is evident, the particles are separated from each other by particle-free intervals. × 40 000.


36b

the distance of the single strands is also higher in our material.

All nonsensory epithelial cells of the vestibular labyrinth seem to be electrotonically coupled by nexuses, as it has been shown for the epithelial cells lining the cochlear duct.

Another membrane specialty which also has been found in the organ of Corti is the rectangular array and this is a very common finding in the vestibular sensory epithelia. Staehelin (1973) described rectangular arrays of A fracture face particles with a center-to-center spacing of approximately 70 Å and complementary pits on the B fracture faces of rat intestinal epithelial cells. These structures were termed "type III" gap junctions. Later on similar rectangular arrays of small particles were observed on the fracture faces of the sarcolemmas of adult rat diaphragm myofibers (Rash et al., 1974). Since these myofibers are separated by basement membranes and are not electrotonically coupled it was concluded that the rectangular arrays of small particles cannot be the morphological or functional equivalents of gap junctions. Similar arrays were observed on freeze-fractured astrocytes (Landis and Reese, 1974) and light cells of the kidney collecting tubule (Humbert et al., 1975). At present, no function is known for the rectangular arrays of small particles. In the astrocytes they have been attributed a possible role in the permeability of the cell membrane (Landis and Reese, 1974). This might be true for the rectangular arrays of supporting cells in both the cochlear and vestibular sensory epithelia. Up to now it cannot be decided, if all supporting cells of the inner ear sensory epithelia are provided with such particle arrays which could be demonstrated in the supranuclear regions of the cells.

Many findings in the vestibular synaptic regions were similar to those in the cochlea which have been described and discussed in part III. A special advantage in the study of the vestibular labyrinth is that the hair cell type I nerve calyx synapse is a synaptic contact of known identity which is thought to be afferent. The B fracture faces of the presynaptic hair cell type I membrane contain aggregations of large particles which we interprete as proteins involved in ion transport. Arrays of small protuberances on the presynaptic B fracture faces and complementary depressions on the A fracture faces have been described in the central nervous system (Akert et al., 1972, Pfenninger et al., 1972, Landis et al., 1974) and also in neuromuscular junctions (Dreyer et al., 1973; Rash and Ellisman, 1974). This prominent specialization of the presynaptic membrane presumably represents the fusion sites between synaptic vesicles and the hair cell membrane where the vesicles release their content of transmitter. Fracture faces of the postsynaptic nerve calyx membrane reveal high number of particles. Such particles are interpreted as the sites of transmitter receptors, or they may be ion channels or enzymes which catalyze neurotransmitter degradation (Landis et al., 1974). However, it would be premature to discuss the functional significance of these findings in detail, because the chemical nature of the afferent inner ear transmitters is still unknown. At present, there is no evidence that electrical synapses also join the hair cell type I to the nerve calyx.

Application of the freeze-fracture technique to the study of vestibular subepithelial blood vessels confirms our findings in the cochlear vessels. The described structures represent the blood-perilymph-barrier. They are of special pathophysiolo-

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Fig. 36b. The tight junction of the same vessel is seen on the B fracture face at higher magnification. Its fine structure is evident, the particles are separated from each other by particle-free intervals. × 60.000.

gical interest if it is supposed that some acute vestibular disturbances in man are due to analogous alterations to those which occur in cochlear vessels in cases of acute hearing loss. On the other hand, resistance changes of the tight junctions of the perilymph-endolymph barrier are thought to develope the equilibrium function disorders in patients with Menierè's disease (see III B)

ABSTRACT

The distribution size and configuration of tight and gap junctions in the guinea pig inner ear were examined in aldehyde-fixed and non fixed freeze etched tissue preparations.

Generally freeze fracture of the zonulae occludentes which seal the endolymphatic space reveals a band of five to eight interconnecting strands. The zonulae occludentes of the cochlear and vestibular sensory epithelia consist of numerous strands and represent the very tight type of junction Possible pathological alterations of the tight junctions in some inner ear diseases are discussed.

The supporting cells of all inner ear sensory epithelia as well as all other epithelia lining the endolymphatic space are coupled by many gap junctions of different sizes. Gap junctions are a common finding on the plasma membranes of the fibrocytes of the spiral ligament and – as previously reported – of all cells of the stria vascularis. Rather seldom they can be observed connecting the cells of the tympanic covering layer

The different particle densities of inner ear cell membranes are described in detail At the base of the stereocilia both in the hair cells of the organ of Corti and in the vestibular hair cell particle aggregations can be found which may be the morphological equivalents of ionic permeability sites and may mediate the first step of the mechano-electric transduction mechanism The kinocilia of the vestibular hair cells exhibit a ciliary necklace (Gilula and Satir 1972)

On the A fracture faces of the supporting cells in all inner ear sensory epithelia rectangular arrays of small particles occur

Preliminary results are reported concerning the hair cell synapses of the cochlea and of the vestibular labyrinth The A fracture faces of the inner ear hair cells show 80-90 Å particles arranged in a thumbprint-like pattern. On the A fracture faces of cochlear and vestibular hair cells rows of particles can be seen. Some synaptic cell membrane features of the inner ear hair cell membranes are similar to those observed in the central nervous system at the sites of chemical transmission e g. aggregations of membrane particles and small protuberances occuring on the B fracture faces of presynaptic membranes (Pfenninger et al., 1972) which are interpreted as temporary fusion sites between synaptic vesicles and the presynapatic membrane. The postsynaptic membranes of the nerve calyx which surround the vestibular hair cell type I show a high particle density on their A fracture faces. These particles are interpreted as transmitter receptors.

The fine structure of freeze-etched inner ear blood vessels is described e.g. their tight junctions, particle densities and micropinocytotic vesicles.

The physiological relevance of the findings is discussed with special respect to the barriers which seal the different compartments of the inner ear (perilymphatic spaces, endolymphatic space stria vascularis) as well as to the blood-perilymph-barrier

ZUSAMMENFASSUNG

Mit der Gefrierätztechnik wurden die Permeabilitätsbarrieren untersucht welche die einzelnen Kompartimente des Meerschweinchen-Innenohres bilden. Vorkommen Ausdehnung und Feinstruktur der interzellulären Verbindungen wie Zonulae occludentes und Nexus wurden beschrieben und ihre funktionelle Bedeutung ausführlich diskutiert. Es wurden weitere neue Befunde an den Zellmembranen des Innenohres und einigen Zellorganellen mitgeteilt die mit dieser Technik zu erhalten waren. Das gilt in besondere für die Sinneszellen der Cochlea und des Vestibularapparates und ihre Synapsen

Grundsätzlich bestehen die Zonulae occludentes der Epithelzellen die den Endolymphraum abschließen und die Perilymph Endolymph-Barriere bilden, aus einem Band von fünf bis acht annähernd parallel verlaufender Leisten ("Zellmembran-Fusions

kalen"). Sie sind somit hinsichtlich des transepithelialen Widerstandes vom "intermediate to tight" Typ. Die Zonulae occludentes der sensorischen Epithelien des Innenohres weisen zahlreiche Leisten auf, im Cortischen Organ 30 und mehr und sind folglich vom "very tight" Typ. Gleiches trifft, wie früher berichtet, auf die "tight junctions" der Basalzellen der Stria vascularis zu, die deren Interzellularräume zu den Perilymphräumen des Ligamentum spirale laterale hin abschließen.

Die Stützzellen der sensorischen und viele Zellen der nichtsensorischen Epithelien des Innenohres sind durch Nexus vermutlich elektrotonisch gekoppelt. Zahlreiche Nexus sind auch an den Fibrozyten des Ligamentum spirale laterale und der subepithelialen Gewebe des Vestibularapparates zu beobachten, sehen an den Mesothelzellen, welche die Scalen der Cochlea auskleiden. Diese Zellen sind durch zahlreiche Desmosomen verbunden.

Als funktionell bisher nicht zu deutender Befund werden rechteckige Anordnungen kleiner intramembranöser Partikel an den Stützzellen der sensorischen Epithelien beschrieben. Besonderes Interesse gilt auch dem Partikelbesatz der Sinneszellen des Innenohres, dessen Anordnung vor allem in den apikalen Zellmembranen Rückschlüsse auf die Membranfunktionen zuläßt. So sind Partikelansammlungen um die Basis der Stereocilien zu erkennen, die als morphologisches Äquivalent der Ionenkanäle gedeutet werden können, welche in den mechano-elektrischen Transduktionsmechanismus der Haarzellen eingeschaltet sind. Im basalen Bereich der Kinocilien-Membranen der vestibulären Haarzellen verlaufen Partikelreihen circulär, die für die Motilität der Kinocilien charakteristisch zu sein scheinen.

Es werden zahlreiche Membrandifferenzierungen der Synapsen des Cortischen Organs und der vestibulären sensorischen Epithelien beschrieben. Die Haarzellen des Cortischen Organs weisen auf ihren A-Flächen Reihen von Partikeln sowie rasterartig angeordnete Partikelformationen auf, auf ihren B-Flächen sind kleine Protuberanzen zu erkennen, die jenen des Zentralnervensystems entsprechen. Gleiches gilt für die B-Flächen der präsynaptischen Membranen des Haarzelltyp I der vestibulären sensorischen Epithelien. Die Protuberanzen sind sowohl in partikelfreien Membranarealen als auch in Aggregationen größerer (etwa 130 Å Durchmesser) Partikel zu beobachten. Diese Partikel sind als Ionen-Pumpen oder Kanäle ~ zu deuten, die Protuberanzen stellen Fusionsort synaptischer Vesikel mit der – präsynaptischen – Haarzellmembran dar. Die A-Flächen der postsynaptischen Membranen der kelchartigen Synapsen des Haarzelltyp I haben eine sehr hohe Dichte relativ homogener Partikel, bei denen es sich um Transmitter Rezeptoren handeln könnte. Weitere Gefrierätzbefunde an den Haarzellsynapsen werden mit denen der Ultradünnschnitt Technik verglichen. Das gilt ebenfalls für die Feinstruktur der diskontinuierlichen Membransysteme der Haarzellen und der Tubuli der Pfeilerzellen der Cortischen Organs.

Die Gefrierätzabdrücke von Blutgefäßen des Innenohres und deren Strukturen wie "tight junctions", Partikeldichte und mikropinocytotische Vesikel werden beschrieben und hinsichtlich der Bedeutung der Blut-Perilymph-Barriere diskutiert.

Schließlich wird auf pathophysiologische Aspekte dieser Untersuchungen eingegangen. So wird z.B. angenommen, daß das fluktuierende Hörvermögen und di. Schwindelattacken bei Morbus Menière durch Widerstandsänderungen der Perilymph-Endolymph-Schranke bzw. ihrer Zonulae occludentes entstehen können.

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Dr med. KLAUS JAHNKE

Univ Hals Nasen-Ohren Klinik

Josef Stelzmann Straße 9

D-5000 Köln 41

Germany

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SUPPLEMENT 337

The Experiment on the Protein Exposed to Acoustic Wave in Model of Hair Cells

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H. TAKEDA

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The Experiment on the Protein Exposed to Acoustic Wave in Model of Hair Cells

BY

H TAKEDA

From Takeda Office of Otolaryngology Fukuoka, Japan

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Abstract

Why do animals have intense troubles mainly in the basal turns of their cochleae by the exposure to sound and the ototoxity? I thought that the protein in cells had an important relation to this subject. So I performed this experiment. I made model of hair cells of silicon and poured three kinds of solutions of protein into them. And I checked the ionization of the protein and its denaturation by giving strong energy of oscillation to them like the same idea of photoelectric effect. As the result as for the protein liquid I noticed the increase of volts just after it was exposed to sound and about 3 hours later I observed the figure decreased gradually From this phenomenon, I presumed that the protein in sensory cells became a factor of the stimulation by receiving strong energy conversely Low-percent protein liquid had less effect caused by sound

Introduction

Why do animals exposed to strong sound have troubles generally in the basal turns of their cochleae? And why are troubles in the inner ears found among the animals administered ototoxic antibiotics such as streptomycin (SM)? How can hair cells feel sound? Why does tinnitus exist? In the auditory mechanism of the inner ear we still have unknown problems today

The Aim of the Study

I think the protein in the epithelial cells of the inner ear has the closest relation to these subjects. When strong energy is given to protein liquid because it is amphoteric electrolyte ionization occurs (Fig 1) positive ions and negative ions separate and it showed some potential. And when much stronger energy works the protein is supposed to be denatured. I think the same phenomenon like this can take place in the protein of the epithelial cells of animals inner ears too.

And from the process of this denaturation, I thought the auditory functions could be presumed conversely so that I had this experi-

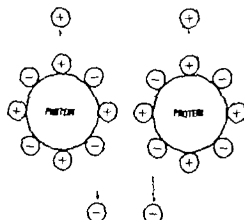


Fig 1 Ionization of protein (Prot.).

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Fig. 4. Sound generator and model of the inner ear

Experiment

I made a model of hair cells in the inner ear and poured a solution of protein into it. According to the law of the energy of oscillation $I = \frac{1}{2}PCW^2A$, I tried to record how the change of W affected the energy

- P Density of medium
- C Velocity of oscillation
- W Frequency
- A Amplitude (sound intensity)

and the reaction of the protein.

I performed two sub-experiments on sound before the main experiment.

Sub-experiment I: Test on exposed sounds

Method

I used the experimental apparatus shown in Fig. 4. 1 kc/s and 4 kc/s as pure sounds were issued from the receiver of an audio-meter *with a certain loudness (90 db)* and I caught them with an electro-condenser microphone *(Sony B. ECM 507702)* and observed them with an oscilloscope. To ascertain the quality of sound and the energy by the difference of frequency, I observed them through (1) a big hole, (2) an ear plug with a fine linear course and moreover (3) an ear plug with a fine spiral course which I made on an experimental basis.

Result

High frequency is hard to go through the fine spiral course. That is to say, the greater the frequency is, the easier it is to be absorbed. In this way, I could make sure of decreasing amplitudes as its physical quality (Fig. 5).

Sub-experiment II: Histological examinations in the inner ears of guinea-pigs

Method

A sound source as shown in Fig. 4 (Leader audio generator, Sony-stereo amplifier 3130F

a

Light (Transverse wave)

Red (Low frequency) 6563.1 A

Blue (High frequency) 4861.3 A

	Red	Blue
Frequency	Low	High
Energy	Large	Small
Amplitude	Large	Small
Photoelectric effect	Bad	Good

(Photoelectric effect is proportional to high frequency)

b

Sound (Wave of condensation and rarefaction)

Low (low frequency) Fairly reflective

High (High frequency) Well absorptive

Fig 2 Properties of wave and oscillation (*a*) Photoelectric effect (*b*) Properties of oscillation in the inner ear The shorter the wave is the more electrons are emitted. Similarity between the photoelectric effect and the inner ear

ment Several kinds of energy of the oscilla tion are used as the strong energy affecting the protein Just like photoelectric effect the more the frequency the stronger the energy (Figs 2 and 3) And when the protein receives it its molecular structure is destroyed

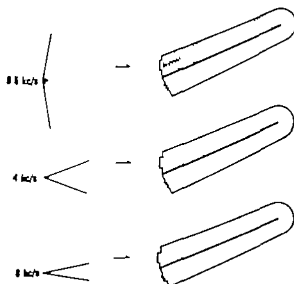
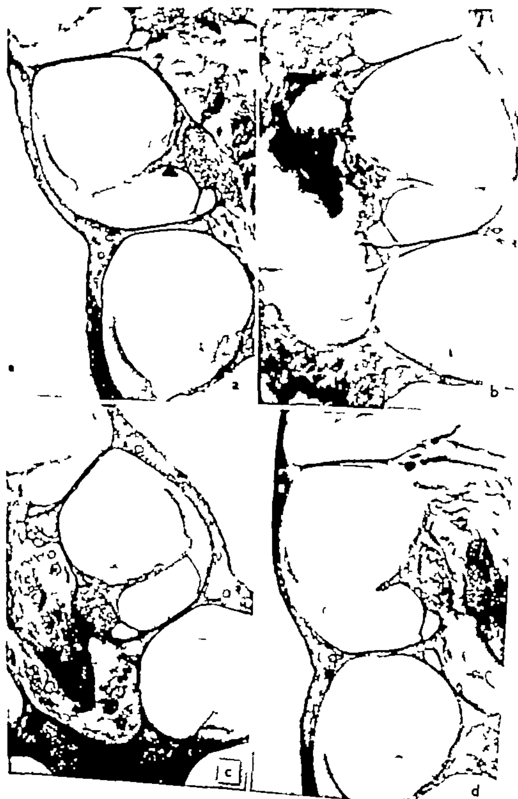


Fig 3 The position and intensity of energy received in the inner ear depends on the difference in frequency


a
b
c
d

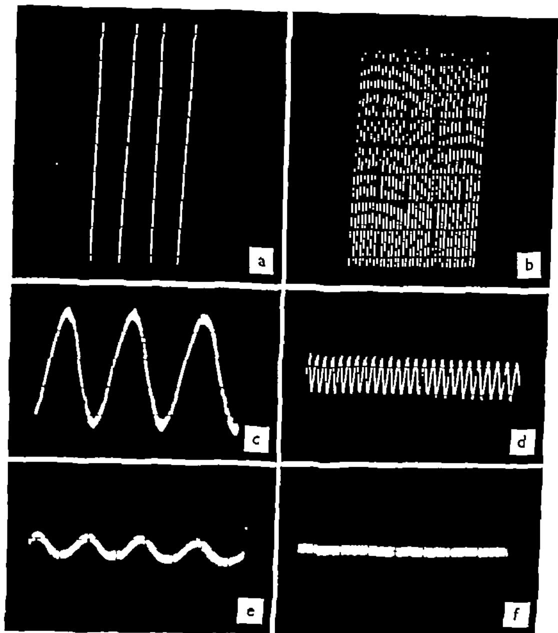


Fig 5 Sound properties in the air (the test in fine air course) (*a*) 0.5 kc/s control (*b*) 4 kc/s control ( ) 0.5 kc/s, a fine linear course (*d*) 4 kc/s fine linear course (*e*) 0.5 kc/s a fine spiral course (*f*) 4 kc/s, fine spiral course It proves difficult to pass along a fine spiral course and is absorbed

Sony stereo preamplifier 2000F) able to issue up to 100 kc/s is used for pure tone and noise from an audio-meter (Trio Audio-Meter Model AS 91) is used for white noise after it is amplified 12 guinea pigs weighing about 100 g were divided into 4 groups—3 to control 3 were exposed to 1 kc/s 3 to 4 kc/s and 3 to white noise I checked the tissues of their inner ears affected by these frequencies After they were placed about 20 cm in front of a loudspeaker and exposed to the loudness of 95 phone 10 hours a day for a week I took out their cochleae and put them in 10% formalin I also made a slice of the cochlear tissue fixed in the

Fig 6 Changes in the organ of Corti caused by sound ( ) Corti apparatus of the guinea-pig (control) (*b*) after exposure to 1 kc/s, 95 phone for 7 days (*c*) after exposure to 4 kc/s 95 phone for 7 days, (*d*) after exposure to white noise for 7 days 1 kc/s destroyed the basal turn the second and the third turn 4 kc/s destroyed mainly the basal turn White noise destroyed mainly the basal turn and the second turn was slightly damaged

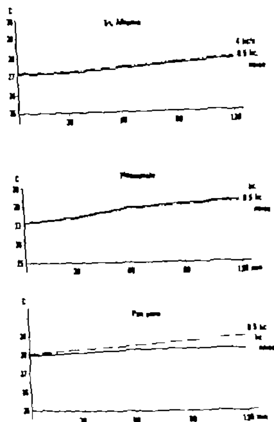


Fig 10 Temperature (slight increase)

Main experiment

Method

As shown in Fig. 4 mentioned above this experiment is to lead the sound of 105 phone issued from an audio-generator and amplified with a loudspeaker through a 2-channel pre amplifier and a 2-channel power-amplifier to the vibrator of the model of hair cells I used 0.5 kc/s 4 kc/s and white noise as exposed sound

That is to say 4 terminals of platinum and 2 mV and μA-meters were used under the DC volts of 80 mV The model of the hair cells was made of a silicon like a column which had a capacity of about 40 cc and at both ends the substitute of vibrator was made of holl and in the center of the model a *pH-meter* and a thermometer were inserted (Fig. 7). 5% human albumin, human plasmanate (preserved in a low temperature about 7°C~8°C) were used as solutions of protein (Table I) The used solutions of protein are simple proteins which generate only amino-acid by the hydrolysis

Result

(*a*) Change of current and volts

I recognized the change of volts in 5% albumin and plasmanate . or 3 minutes after sound was exposed in a solution of protein and the values were low in the order of white noise 4 kc/s and 0.5 kc/s and the time of reaction was different each time But I could not recognize a significant change in electric current (Table II Figs 8 and 9)

(*b*) Change of temperature in the protein liquid

Because temperature absorbs the energy of sound a little increase was admitted in 5% albumin plasmanate and pan-amin But there was no change by the difference of frequency (Fig. 10)

(*c*) Change of pH in the protein liquid

In 5% albumin (pH 7 1) there was a little increase of pH after it was exposed to white noise and on the other hand there was no change or a tendency of decreasing to 0.5 kc/s and 4 kc/s. In plasmanate (pH 6.59) and pan-amin (pH 5 9?) there existed a tendency of increasing just a little (Fig 11)

Table I *Ingredients of applied protein liquid*

Albumin (5%)	Plasmanate	Pan-amin (W/V %)
1 100 ml (Na. 2 5 mEq) pH 6 9±0.5	Albumin, 8.8% γ-Globulin, 7% β-Globulin, 5% *in 100 ml*	l-Arginine, 0 27
		l-Histidine 0.13
		l-Isoleucine, 0.18
		l-Leucine 0.41
	Na. 112 0 mEq Cl: 50.0 mEq K. 0.5 mEq	l-Lysine, 0 6.
		l-Methionine, 0.24
		l-Phenyl-alanine 0.29
	pH 6 59	l-Threonine, 0 18
		l-Tryptophan, 0 06
		l-Valine 0.20
		Glycine, 0.34
		Dextran 70, 6 00
		pH. 5.92

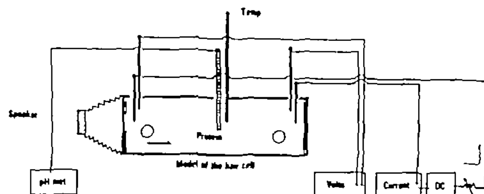


Fig 7 The apparatus for the ionization test of protein The construction was of silicone and had a capacity of 40 cc, a length of 10 cm and a diameter of ...5 cm.

Zelloidin liquid like a pattern after it was dyed in the Haematoxylin Eosin (H E) and I made a microscopic inspection of it

Result

I recognized 1 kc/s caused trouble in their first second and third turns of the three guinea pigs and 4 kc/s caused trouble in the first turn and under the exposure of white noise mainly in the first turn and a little trouble in the second turn (Fig 6) As for the opinions on the troubles in the inner ear caused by pure tone and white noise they are almost the same as the reports in the past (Kawata 1955 Takeda 1960)

The aim of this histological examination is to check the troubled regions of the cochlea and its extent caused by the energy when the frequency was changed and on the other hand the loudness is fixed

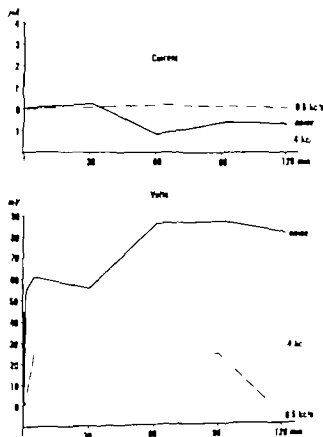


Fig 8 The increase in voltage in the albumin.

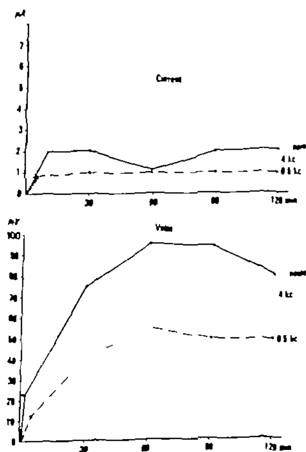


Fig 9 The increase in voltage in the plasmanate

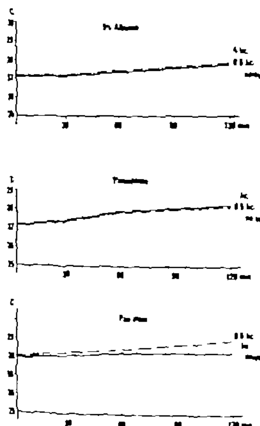


Fig. 10 Temperature (slight increase)

Main experiment

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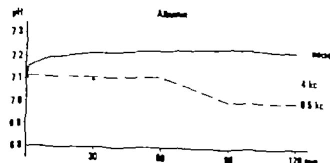
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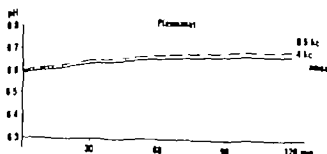
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In 100 ml (Na 2.5 mEq) pH. 6 9±0.5	Albumin, 8 8% γ-Globulin, 7% β-Globulin, 5% in 100 ml Na. 11_0 mEq Cl 50 0 mEq K. 0.5 mEq pH. 6 49	l-Arginine, 0.27 l-Histidine, 0 13 l-Isoleucine, 0.18 l-Leucine, 0 41 l-Lysine, 0 6_ l-Methionine, 0.24 l-Phenyl-alanine, 0 29 l-Threonine, 0.18 l-Tryptophan, 0.06 l-Valine 0.30 Glycine, 0.34 Dextran 70 6 00 pH 5.92





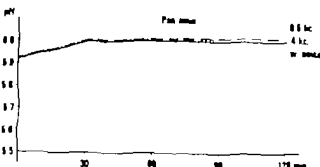
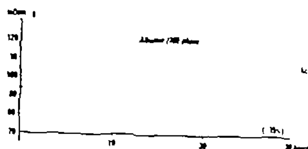
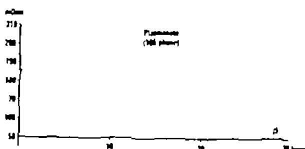


Fig 11 pH test (slight increase or no hange)





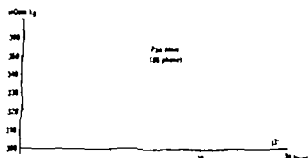


Fig 12 Change n osmoti pressure Significant change wa detected in albumin 30 hours after the exposure to sound

Table II *Change of volts by the stimulation of sound with the passing of time—the numerical value is mean*

Solution of protein	E posure under 105 phone	Time (min)					
		1	5	30	60	90	120
Albumin (5%)	0.5 kc/s	6 5	5 0	40 0	70 0	— 5	— 5
	4 kc/s	6.0	1 5	46 0	49 5	38 5	28 0
	White noise	54 0	61 0	56 5	86 0	88 5	82.5
Plasmanate	0 5 kc/	0 0	1 5	40 0	55 0	50 0	50 0
	4 kc/s	2.5	4 5	62.5	77 5	75 0	70 0
	White noise	2. 0	32 5	75 0	95 0	95 0	80 0
Pan-amin	0.5 kc/s	25 0	25 0	26.0	28 0	28 5	29 0
	4 kc/s	27 0	27.5	27 5	28.0	27 0	26 5
	White noise	28 0	27 0	27 0	28 0	28 0	28 0

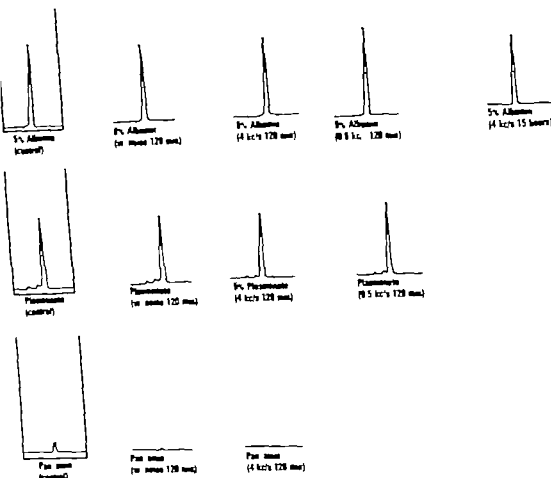


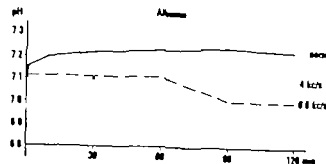
Fig. 13. Change in the electrophoretic test. The albumin curve began to fall from its peak 15 hours after the exposure to sound (right side).

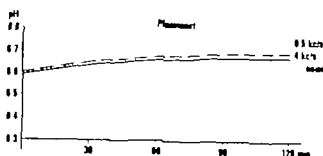
(*d*) Denaturation test on the proteins

There was almost no change in osmotic pressure, viscosity and electrophoretic test 2 hours after the protein liquid was exposed to sound. But in 5% albumin there was a change of value of osmotic pressure (osmolality) 20 hours later and after 30 hours there could be found a significant change (94 mOsm/kg $H_2O \rightarrow 108$ mOsm/kg H_2O) (Fig. 12). However, as for viscosity and electrophoretic test, distinct change could not be found (Fig. 13).

Discussion

As stated above, when strong energy is given to a solution of protein, its denaturation occurs. "Basic Chemistry" (Ogawa et al. 1953) made it clear already. In the process as far as denaturation, I expected the ionization of amphoteric electrolyte and caught the ionization phenomenon as the change of volts. This probably means that the electric charge of





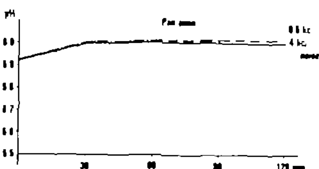
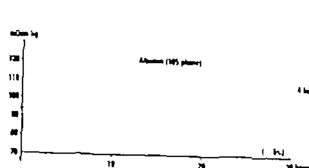
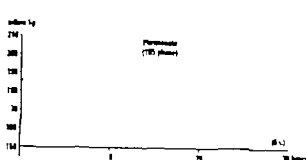


Fig. 11. pH test (slight increase or no change)





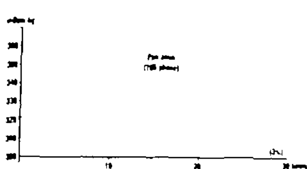


Fig. 12. Change in osmotic pressure. Significant change was detected in albumin 30 hours after the exposure to sound.

Table II. *Change of volts by the stimulation of sound with the passing of time—the numerical value is mean*

Solution of protein	Exposure under 105 phone	Time (min) 1	5	30	60	90	120
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	4 kc/s	6.0	1[illegible].5	46.0	49.5	38.5	28.0
	White noise	54.0	61.0	56.5	86.0	88.5	82.5
Plasmanate	0.5 kc/s	0.0	12.5	40.0	55.0	90.0	90.0
	4 kc/s	[illegible]5	42.5	6[illegible].5	72.5	75.0	70.0
	White noise	22.0	3[illegible].5	75.0	95.0	95.0	80.0
Pan-amin	0.5 kc/s	25.0	[illegible]5.0	[illegible]6.0	28.0	28.5	29.0
	4 kc/s	7.0	27.5	[illegible]7.5	28.0	27.0	[illegible]6.5
	White noise	28.0	27.0	7.0	28.0	28.0	28.0

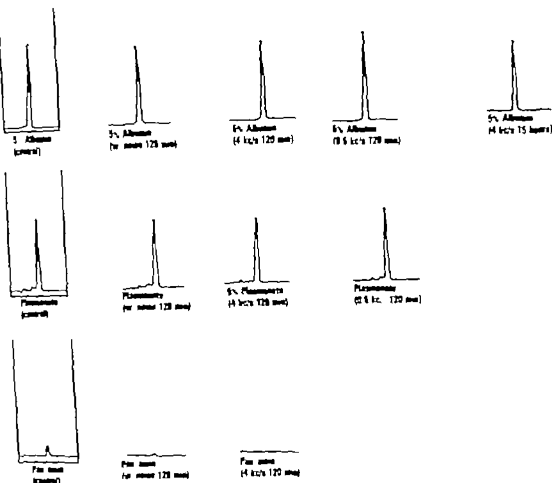


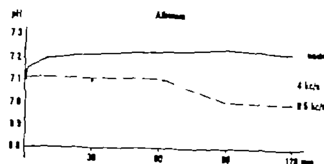
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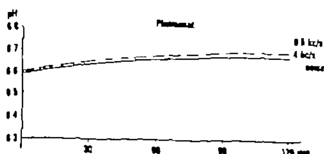
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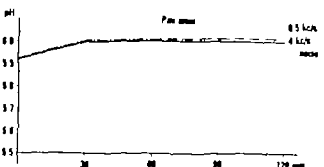
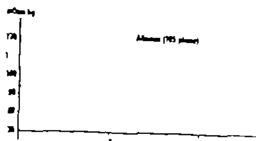
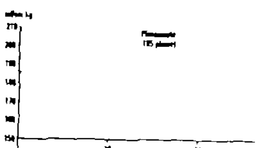


Fig. 11. pH test (slight increase or no change).





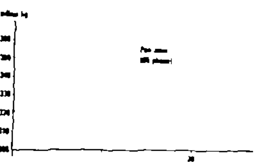


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	White noise	22.0	32 5	75 0	95 0	95 0	80 0
Pan-amin	0.5 kc/s	25 0	25 0	26 0	28 0	28.5	29 0
	4 kc/s	77 0	27 5	77 5	28 0	27 0	76 5
	White noise	28 0	27 0	27 0	28 0	28 0	28 0

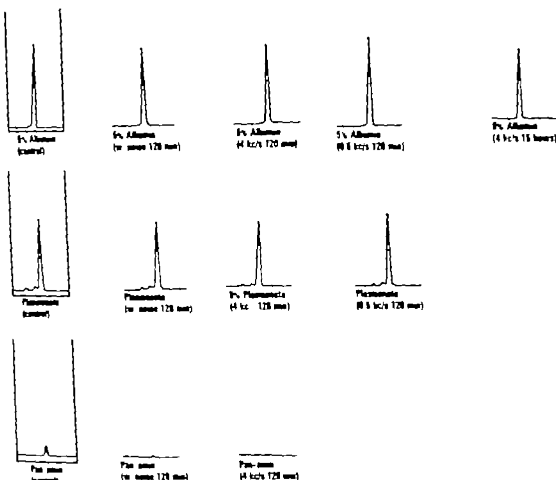


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There was almost no change in osmotic pressure viscosity and electrophoretic test 2 hours after the protein liquid was exposed to sound. But in 5% albumin there was a change of value of osmotic pressure (osmolality) 20 hours later and after 30 hours there could be found a significant change (94 mOsm/kg $H_2O \rightarrow 108$ mOsm/kg H_2O) (Fig. 12) However as for viscosity and electrophoretic test distinct change could not be found (Fig. 13)

Discussion

As stated above when strong energy is given to a solution of protein, its denaturation occurs. Basic Chemistry (Ogawa et al. 1953) made it clear already In the process as far as denaturation, I expected the ionization of amphoteric electrolyte and caught the ionization phenomenon as the change of volts. This probably means that the electric charge of

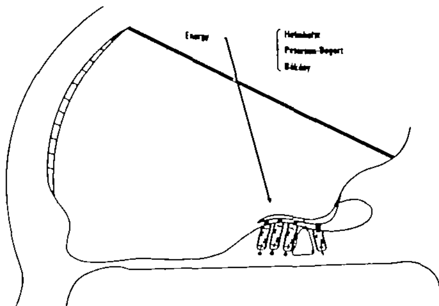


Fig 14 The hair cell model may be replaced by the inner ear in Fig. 14

positive and negative ions on the surface of the protein generates the flow of ions under the DC volts of 80 mV by giving the energy of oscillation to the protein through the vibrator But this phenomenon will be irreversible when the energy of oscillation lasts long and becomes strong, the particles of protein swell the viscosity increases the solubility decreases and the osmotic pressure increases My model is incomparatively bigger than the capacity of real hair cell in the inner ear It is a matter of course that the value of volts depends on the size of the model and the quality of the vibrator and the kinds of protein Therefore the functions of protein in the hair cells of the inner ear cannot be presumed through the results of this experiment But under a certain condition it is no doubt that a solution of protein can be ionized at least In 1954 Békésy assumed a transformer as a hair cell and the ionization of protein may be a reason And according to recent literature it is said that the troubles in the hair cells by ototoxic antibiotics of aminoglycoside group such as SM KM and so on are strongly effected by the denaturation of mitochondria in cells (Nakai et al 1971) It seems to me that it is in accord with the theory of basic chemistry which says these ototoxic antibiotics are the reactions stopping protein synthesis (Morino et al 1973)

Well what kind of relation does the quality of protein easily denatured by this kind of energy have with the trouble of the inner ear caused by sound and ototoxity? I will explain it in Chart 1

From the above-mentioned experiments

(1) It is supposed that the basal turn of cochlea receive strong energy by the structure and the quality of oscillation So the trouble caused by the exposure of sound and ototoxity is distinct in the basal turn

(2) Protein is ionized by the action of strong energy and when the action lasts long it is denatured Moreover it is presumed that this must be a close relation to audition vision thermesthesia and tactile sensation Next checking the change of pH there is a little tendency of transferring to alkali in albumin plasmanate and pan-amin I think this is because positive and negative ions of proteins are light electrolyte



Chart 1

Summary

To catch the ionization of protein 105 phone energy of oscillation was given to 0.5 kc/s 4 kc/s and white noise exposed in 5% albumin plasmanate and pan-amin I checked volts current, pH temperature and so on about them. Distinct change of volts was found in the albumin and the plasmanate which contained much protein. The value of volts stayed high for about 3 hours after they were stimulated, but with the passing of time it went down slowly The model of hair cells may be replaced by the inner ear in Fig. 14

From this phenomenon of ionization, I think I can presume the auditory mechanism of the hair cells of inner ear conversely As for the denaturation of protein I noticed a change of osmotic pressure about 30 hours after they were exposed to sound As mentioned above I think the action of energy which lasts long denatures protein and causes troubles in the inner ear (especially in basal turn)

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Introduction

In the field of clinical laryngology indirect laryngoscopy is used as a routine method of examining patients Significant observations of the larynx can be obtained through this method including observations of the adductive and abductive movements of the vocal folds and of the arytenoids. Indirect laryngoscopy however has several shortcomings. It needs some skill on the part of the clinician and since the interpretation of the findings obtained by this method are more or less subjective diagnoses obtained by different laryngologists through indirect laryngoscopy alone may sometimes be inconsistent or even incompatible Pathologic changes beneath the true vocal folds are frequently overlooked The rapid vibratory motions of the vocal folds cannot be observed by conventional laryngoscopy Also there are certain patients on whom indirect laryngoscopy cannot be performed adequately because of an anatomical or a physiological abnormality or because of dyspnea.

In addition to indirect laryngoscopy direct laryngoscopy or special X-ray examinations such as laryngography may be used as supplementary methods for examining the larynx These supplementary methods however usually result in some discomfort or danger to the patient. Therefore a technique which can provide adequate laryngeal information with less discomfort or risk should be of significant help to clinical practice Diagnosis through the voices of patients, for example may fulfill this prerequisite because uttering voiced sounds can be done without any difficulty by most patients. Hence if it can be proved that voices of patients carry sufficient information for differentiating various laryngeal pathologies diagnosis by analyses of patients voices would be a useful supplement to indirect laryngoscopy

The voice can convey *information other* than meaning, such as sex, age and the emotional state of the utterer Furthermore in many cases an identification of the speaker may be made through speech As voice is a kind of sound it seems reasonable to assume that its basic perceptual characteristics are pitch loudness length and timber which correspond to known fundamental acoustical features. The overall number of perceptual cues seems to be rather limited Since man can recognize a variety of objects as mentioned above using a limited number of perceptual cues, it is quite possible that individual perceptual cues are used in recognition in different ways.

The acoustic characteristics of speech may be classified into two elements i e variable and invariable. For example while the possible maximum and minimum fundamental frequency of a person s voice is physiologically limited he can utter a voiced sound of any arbitrary frequency within this limit. The fundamental frequency of phonation here represents a variable element, while the upper or lower limit of the vocal range constitutes an invariable element. The same holds true with duration and intensity of voicing. Since the characteristics to be investigated for detecting laryngeal pathology should be invariable ele

ments that is abnormal acoustic features corresponding to certain pathologic changes in the larynx it may appear that such variable elements as fundamental frequency intensity duration etc are not distinctive cues for this purpose

Many investigators have therefore attempted to find invariable acoustic parameters which might correspond to laryngeal pathologies The parameters investigated have included the elevated levels of noise components and the loss of harmonic components in spectrograms of pathologic voices (Nessel 1960 Yanagihara 1967) increased pitch or frequency perturbation in acoustic waves of pathologic voices (Lieberman 1963 Smith & Lieberman 1964 Hiki et al 1967 Koike 1967 Iwata & von Leden 1970 Hecker & Kreul 1971) and information included in amplitude perturbation (Koike 1969) Although these studies provided considerable hope for the use of acoustic methods for detecting laryngeal lesions the results of these studies still seem to be insufficient for the purposes of categorization or of differential diagnosis of laryngeal diseases

On the other hand it is known that experienced laryngologists are to a considerable extent capable of diagnosing laryngeal diseases simply by listening to the voice of a patient There is a strong possibility that laryngologists are utilizing many acoustic parameters which have not yet been accounted for by the above mentioned acoustic studies when they make diagnosis of a laryngeal disease through use of a vocal cue

The terms for expressing the impressions of pathologic voices by laryngologists may be *hoarse harsh breathy* etc These terms however do not seem to be pertinent to differentiating laryngeal pathologies because the definitions of these terms are subjective and indistinct In order to elucidate the mechanism of diagnosing laryngeal diseases by voice therefore some perceptual studies seem to be needed and the use of precise psychometric procedures is required The methods relevant to this purpose may include paired comparison triadic comparison and the semantic differential techniques

Among these procedures the semantic differential technique proposed by Osgood et al (1957) has been utilized by several investigators for studying the auditory impression of human voice and speech Voiers (1964) found 4 perceptual factors from short speech samples from 16 men He labeled these factors as "clarity" or "intelligibility roughness "magnitude and "speech rate respectively Holmgren (1967) found that speakers voice characteristics can be accounted for by two basic factors as determined by listener judgments alone and referred to the factors as "loudness and pitch With the use of speech samples from 100 males and 100 females Silbiger (1966 1969) studied the perceptual classification of voices and reported that the analyses provided an excellent three-dimensional fit Besides he found that the ratings on the semantic differential represented the perception of the voice quality and were not dependent upon extraneous factors such as language difference Clarke & Becker (1969) extracted 4 factors from the spoken sentences of 8 male speakers By applying the semantic differential technique with 17 pairs of Japanese adjectives Isshiki et al (1969 1970) made a perceptual study of hoarseness They stated that analyses of the data with the use of D-factoring revealed 4 factors which they labeled as Factor R (rough) Factor B (breathy) Factor A (asthenic) and Factor D (degree) respectively Based on this result they proposed a simplified rating method for the classification of hoarseness

There have also been studies attempting to relate perceptual characteristics to certain acoustic properties of speech Emanuel & Sansone (1969) Sansone & Emanuel (1970) and Lively & Sansone (1970) for example tried to relate the auditory characters of simulated rough or harsh voice to spectral noise levels Wendahl (1963 1966*a b*) investigated the relations between pitch or amplitude per

turbation and perceptual impressions of synthesized voices. Coleman (1971) has studied the effect of waveform changes of simulated glottal waves upon the perception of roughness.

Although these studies have yielded some interesting results knowledge in this area still seems to be limited. It seems that there is an obvious need of conducting some perceptual studies in order to refine the procedures of judging voice quality in dealing with patients with laryngeal pathology and to relate the resulting perceptual cues to certain acoustic parameters which may be relevant to laryngeal pathologies It is hoped that this type of study will be of some help in ultimately establishing some diagnostics to supplement indirect laryngoscopy

The semantic differential technique was employed in the present study as a psychometric procedure because of its simplicity as in the cases of other studies described above Needless to say this selection does not imply that the semantic differential procedure is most appropriate for investigating the perceptual structure of voice quality It is rather apparent that this technique has some *limitations* Among others it should be noted that dimensions extracted with this technique are more or less dependent upon the pairs of words used to define the scales. Since this technique can provide an objective and accurate orthogonal basis for the data space nevertheless the adoption of the semantic differential technique seemed to be justifiable under certain conditions. A more powerful means of data collection and analysis may eventually prove useful, however in understanding the more detailed structure of speech perception

Method

A. SEMANTIC DIFFERENTIAL SCALES

1 English scales

As the scales for listener judgments 1 pairs of polar-opposite adjectives assumed to be most related to the judgment of voice quality were selected from the list of 50 pairs of words used by Osgood et al They were (1) nice–awful (2) sweet–sour (3) clean–dirty (4) happy–sad, (5) strong–weak, (6) large–small (7) heavy–light, (8) hard–soft, (9) fast–slow (10) active–passive (11) sharp–dull and (12) hot–cold

The first four pairs represented an *evaluation* factor the second four pairs a *potency* factor and the last four indicated an *activity* factor as described in the analysis of general concepts by Osgood et al. It should be mentioned however that these scales were selected rather arbitrarily and that there is no assurance that these scales are all pertinent to the perception of acoustic stimuli such as voice. A better selection of adjectives might be feasible in further study which may in turn explicate a more detailed structure of perception of pathologic voices. Also whether the factors derived from these scales correspond to such psychological characteristics as evaluation, potency etc is still to be determined

1 ·ws

2. Japanese scales

In order to investigate the inter-cultural validity of this kind of study the 12 English scales were translated word-for word into Japanese adjective pairs They were (1) yoi–warui (2) amai–suppai (3) kireina–kitanai (4) shiawasena–fushiawasena, (5) tsuyoi–yowai (6) okii–chiisai (7) omoi–karui, (8) katai–yawarakai (9) hayai–osoi (10) sekkyokutekina–shokyokutekina, (11) surudoi–nibui, and (12) atsui–

Table I *Laryngeal status age sex mean breathy score mean rough score and the values of three acoustic parameters for 15 pathologic (P) and 9 normal (N) subjects*

Sample no	Laryngeal status	Age	Sex	Mean breathy score	Mean rough score	FF (Hz)	FPQ	APQ
P 1	Extended cancer	50	♂	_5	4	155	$68.7\times10^{-}$	170.1×10^{-4}
P	Nodule	40	♂	0.5		137	8 7	18.5
P 3	Unilateral paralysis	44	♂	1.5	3.5	49	83.2	110.9
P-4	Chronic laryngiti	44	♀	0.5	1.5	103	6.9	_6
P 5	Unilateral paralysis	55	♂		3.5	137	7	111 8
P-6	Bilateral paralysis	37	♂	0	1	88	4 2	_5.3
P 7	Partial-laryngectomized	76	♂	4	_5	104	67 0	90
P-8	Nodule	11	♂	1	2	771	1_0	28.5
P 9	Tumor	61	♀	0	3.5	149	102_	137.3
P 10	Laryngeal stenosis (trauma)	60	♀	3	_5	88	45 ?	110 0
P 11	Chronic laryngitis	48	♀	0.5		284	7.8	10.9
P 1	Nodule	33	♀			305	17 9	38.3
P 13	Hemilaryngectomized	56	♂	3	4	96	76.1	96.0
P 14	Contact nodule	69	♂	1	_5	100	8.0	63.5
P 15	Unilateral paralysis	53	♀	4	3	–	–	–
N 1	Normal	33	♂	0	1.5	103	5 0	56.4
N	Normal	_3	♂	0	0 5	110	5 0	39 0
N 3	Normal	28	♂	0	_5	119	4 8	46.0
N-4	Normal	_3	♀	0		_32	6.5	18.1
N 5	Normal	31	♂	0	1 5	113	8.6	38.5
N-6	Normal	79	♂	1	1 5	93	4 9	_3.3
N 7	Normal	_3	♂	1	0 5	128	6.2	55 6
N-8	Normal	36	♀	1.5	0	180	5 7	47 7
N 9	Normal	77	♂	0	1	91	3 7	14

– not measurable

tsumetai The same test stimuli were subjected *to a separate listening test with the use of these* Japanese scales

B TEST STIMULI

1 *Voiced samples*

The first set of stimuli consisted of samples of the vowel [a] *tape recorded from 24 subjects 9 normal persons and 15 patients with various* laryngeal diseases as shown in Table I There were 16 males and 8 females ranging in age from 11 to 76 After the speech recording was made the laryngeal status was derived by conventional *indirect laryngoscopy In some* cases surface anesthesia was needed

The subjects were instructed to sustain the vowel [a] for several seconds at the most comfortable pitch and loudness Magnetic tape recordings *of the voices were obtained concurrently in two different ways* The acoustic speech waveform from a dynamic microphone (Electrovoice 666) positioned in front of the *subject s mouth was recorded on one channel* of a dual channel tape recorder (Ampex AG 600-2) The acoustic signal from a small con*denser microphone (Brüel & Kjaer 4136)* coupled to the pretracheal skin of the subject was recorded on the other channel of the tape recorder The recorded acoustic speech wave form was employed for the listening tests *while the recording from the pretracheal signal* was used for the measurement of the acoustic parameters described below

From the voices recorded on the first channel *segments of approximately* 1 5 sec duration were chosen out of the most constant parts of the vowels Each of these segments was rerecorded 14 times at the same intensity on a separate tape recorder Approximately 2 5 sec of silence was given between the successive stimuli The intensities of the different voices were also adjusted to be the same As a result *each voice sample used in*

his study contained neither an initiation nor a termination and was almost constant. However some degree of fluctuation in both fundamental frequency and intensity within a sample was inevitable in some of the pathologic voices. The order of the presentation of the stimuli was randomized

The fundamental frequency (FF) a frequency perturbation quotient (FPQ) and an amplitude perturbation quotient (APQ) were analyzed from the contact microphone signals corresponding to the voice samples used for the listening tests. The FPQ was defined as an averaged and normalized perturbation of the peak-to-peak pitch periods. The frequency perturbation quotient is defined as

$$FPQ = \frac{\frac{1}{n-3}\sum_{i=2}^{n-2}\left|\frac{F_{i-1}+F_i+F_{i+1}}{3}-F_i\right|}{\frac{1}{n-1}\sum_{i=1}^{n-1}F_i}$$

where n indicates the number of period peaks and F represents the instantaneous frequency value defined as the inverse of the period length.

The APQ stood for a similarly averaged and normalized rate of variation in the peak amplitude It is defined to be

$$APQ = \frac{\frac{1}{n-11}\sum_{i=6}^{n-5}\left|\frac{A_{i-5}+A_{i-4}+\cdots+A_i+\cdots+A_{i+5}}{11}-A_i\right|}{\frac{1}{n-1}\sum_{i=1}^{n-1}A_i}$$

where A depicts the peak-to-peak amplitude of the fundamental period Detailed discussion on these acoustic parameters will be found elsewhere (Koike Takahashi & Calcaterra) The values of the acoustic parameters together with the laryngeal status age sex, and breathy and rough scores of the subjects are shown in Table I The explanation for the breathy and rough scores will be found below

2. Synthesized samples

The second set of stimuli consisted of synthesized vowel samples generated by a cascade type terminal analog synthesizer which was controlled by a PDP-8 digital computer A detailed description of this synthesis method is found elsewhere (Flanagan 1965) The frequencies of the first four formants were specified as 750 1250 2550 and 3000 Hz and their respective bandwidths were 60 80 100 and 200 Hz. A total of 9 samples having three different fundamental frequencies (100 Hz for low 205 Hz for medium and 300 Hz for high) at three different intensities separated by 5 dB steps (weak, medium and strong) were generated and recorded on a tape recorder (Ampex AG 600-2) Each sample was of 1.5 sec duration and was repeated 14 times at an interval of 2.5 sec.

C LISTENING TESTS

For the listening tests 6 different kinds of test sheets were prepared The 12 scales were randomized in terms of order and polarity The order of the sheets was also randomized for different listeners. This preparation was done for both the English and Japanese scales.

The listening tape was reproduced through a loud speaker (Ampex AA 620) in such a way that the same stimulus was repeated 14 times successively The sound pressure level of the stimulus at the listeners ears was approximately 75 dB re 0 0002 dyne/cm² The order of presentation of the different voices was randomly arranged in order to minimize the preoccupation of the subjects. Listeners rated their auditory impressions on the test tones against the 12 seven-point scales. During the course of instructions the listeners were asked to hear several repetitions of a sample However no further exercises were made before the rating task. Listeners were then requested to mark their first impression promptly

The listeners were selected from the laboratory staff who had normal hearing. In judging with the English scales 11 adults ranging in age from 23 to 41 including two females were adopted. Although they were scientists from various fields, none of them had notable ex

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P 3	Unilateral paralysis	43	♂	1 5	3 5	249	83 2	110.9
P-4	*Chronic laryngitis*	44	♀	0.5	1.5	103	6.9	22 6
P 5	Unilateral paralysis	55	♂	2	3.5	137	7	111.8
P-6	Bilateral paralysis	37	♂	0	1	88	4	53
P-7	Partial-laryngectomized	76	♂	4	.5	104	67 0	90
P-8	Nodule	11	♂	1		771	1.0	28.5
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P 10	Laryngeal stenosis (trauma)	60	♀	3	.5	88	45	110.0
P-11	*Chronic laryngitis*	48	♀	0.5	2	284	7 8	10 9
P-12	Nodule	33	♀	2	2	205	17 9	38.3
P 13	*Hemilaryngectomized*	56	♂	3	4	96	26.1	96.0
P 14	Contact nodule	69	♂	1	2.5	100	8.0	63.5
P 15	*Unilateral paralysis*	53	♀	4	3	–	–	–
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where n indicates the number of period peaks, and F represents the instantaneous frequency value defined as the inverse of the period length.

The APQ stood for a similarly averaged and normalized rate of variation in the peak amplitude It is defined to be

$$\mathrm{APQ} = \frac{\frac{1}{-11}\sum \frac{A \quad + A_{i+4} + \quad + A + \quad + A_{i}}{11} - A}{\frac{1}{-1}\sum A}$$

where A_i depicts the peak-to-peak amplitude of the fundamental period Detailed discussion on these acoustic parameters will be found elsewhere (Koike Takahashi & Calcaterra) The values of the acoustic parameters together with the laryngeal status, age, sex, and breathy and rough scores of the subjects are shown in Table I The explanation for the breathy and rough scores will be found below

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N	Normal	.3	♂	0	0 5	110	5 0	39 0
N 3	Normal	.8	♂	0	.5	119	4 8	46.0
N-4	Normal	23	♀	0		.32	6 5	18 1
N 5	Normal	31	♂	0	1.5	113	8 6	38.5
N-6	Normal	79	♂	1	1 5	93	4 9	.5 3
N 7	Normal	23	♂	1	0 5	128	6.	55 6
N-8	Normal	36	♀	1 5	0	180	5 7	47 7
N 9	Normal	77	♂	0	1	91	5 7	21 4

– not measurable

tsumetai The same test stimuli were subjected to a separate listening test with the use of these Japanese scales

B TEST STIMULi

1 Voiced samples

The first set of stimuli consisted of samples of the vowel [a] tape recorded from 24 subjects 9 normal persons and 15 patients with various laryngeal diseases as shown in Table I There were 16 males and 8 females ranging in age from 11 to 76 After the speech recording was made the laryngeal status was derived by con ventional indirect laryngoscopy In some cases surface anesthesia was needed

The subjects were instructed to sustain the vowel [a] for several seconds at the most com fortable pitch and loudness Magnetic tape re cordings of the voices were obtained concur rently in two different ways The acoustic speech waveform from a dynamic microphone (Electrovoice 666) positioned in front of the subject s mouth was recorded on one channel of a dual channel tape recorder (Ampex AG 600-2) The acoustic signal from a small con denser microphone (Brüel & Kjaer 4136) coupled to the pretracheal skin of the subject was recorded on the other channel of the tape recorder The recorded acoustic speech wave form was employed for the listening tests while the recording from the pretracheal signal was used for the measurement of the acoustic parameters described below

From the voices recorded on the first chan nel segments of approximately 1 5 sec dura tion were chosen out of the most constant parts of the vowels Each of these segments was rerecorded 14 times at the same intensity on a separate tape recorder Approximately 2 5 sec of silence was given between the suc cessive stimuli The intensities of the dif ferent voices were also adjusted to be the same As a result each voice sample used in

scribing the perceptual abnormality of patients voices in rather separate senses It was thought to be interesting to compare such clinical gradings with the semantic differential ratings on the same utterances. It should be mentioned, however that aside from the fact that these terms are most commonly used and widely understood by laryngologists they are merely examples and have been otherwise arbitrarily chosen from many expressions adopted in clinical descriptions. Many other selections should be feasible in future investigations.

D FACTOR ANALYSIS PROCEDURES

The data obtained were analyzed with either one of the two factor analytic methods Le D-method of factoring (Osgood et al 1957) and Lawley s maximum likelihood method (Lawley & Maxwell 1963) with Kaiser s varimax rotation (Kaiser 1958) Both methods were applied to some of the data (mainly those on natural voice samples) for comparison

In the following discussion, the word "dimension" will be used for the results of the D-method, while the word "factor" will be adopted for the results of the Lawley method

Results

A. RELIABILITY

Prior to the detailed analysis of the data, the reliability of the judgments was examined. As an indicator for dispersion of the rating score the square root of the unbiased variance or sample standard deviation (S D) was calculated for each scale for every voice Though the square root of the unbiased variance may not represent the strict inter listener reliability a small value should suggest a high degree of agreement among the listeners if the mean value is also taken into account Although there were certain judgments which revealed considerable S D values (for example 2.07 for P 1 on the strong–weak scale or 2 00 for P 5 on the heavy–light scale) most of the S D values were found to be in the range of 0.5 to 1.5 suggesting that the rating scores do indeed center closely around their mean values The agreement therefore seemed to be sufficient for the purpose of the present study

Test 1 and test were performed at an interval of 3 months which was thought to be a long period Six of the 8 listeners engaged in test 1 were also listeners for test 2. Since the voices of P 1 and P 5 were used in both tests, those 6 listeners rated their auditory impression on these selected pathologic voices on two occasions separated by a considerable time interval The correlation coefficient between the corresponding rating scores made

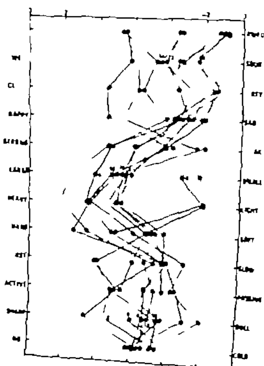


Fig 3 Profiles of mean rating scores for 10 pathologic voices on 12 adjective scales for test 3

perience in listening tests It seemed justifiable to regard them therefore as untrained naive judges In rating with the Japanese scales a group of 15 Japanese otolaryngologists who had no experience in listening experiments were employed They were all males between 26 and 41 in age but since they were pre dominantly in training in laryngology and did not yet have long-term experience with lis tening to pathologic voices they were also re garded as inexperienced naive listeners

A total of five listening tests were per formed The first four tests were on the Eng lish scales and the fifth was on the Japanese scales In the first test 8 listeners rated 5 pathologic voices (P 1 to P 5 in Table I) and one normal voice (N 1) In the second test 11 judges evaluated 8 normal (N 2 to N 9) and two pathologic (P 1 and P 5) voices The listeners were not notified in advance of the

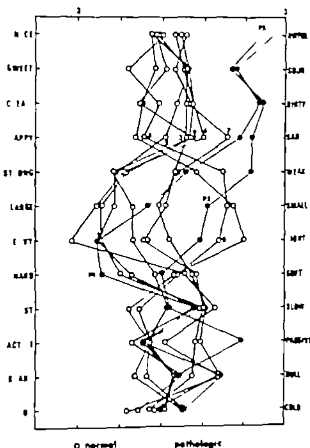


Fig 2 Profiles of mean rating scores for 8 normal and pathologic voices on 1 adjecti e scales for test –

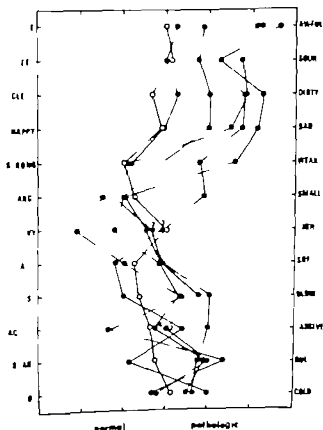


Fig 1 Profiles of mean rating scores for one normal and 5 pathologic voices on 1 adjective scales for test 1

tests that the stimuli included the signals pro duced by normal speakers In the third test 8 subjects judged 10 pathologic voices (P-6 to P 15) The synthesized samples were em ployed in the 4th listening test At the be ginning of this test the medium frequency" and medium intensity sample was presented 14 times as the reference sound The listeners however were not informed that the presenta tion was for reference Nine subjects per formed the rating task on English scales In the 5th test the 24 voice samples from the 15 pathologic and 9 normal subjects mentioned above were presented to the Japanese listeners and were rated in one listening session

In addition to the listening tests just de scribed two laryngologists evaluated all the voice samples in terms of breathiness and roughness These terms breathy and rough are most commonly employed in clinics for de

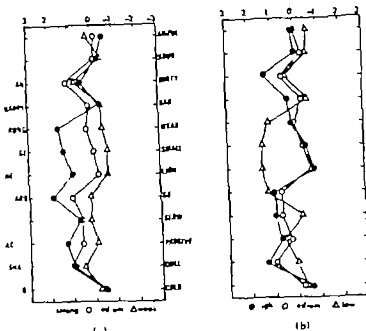


Fig. 5. (*a*) Profiles of mean rating scores for three synthesized samples with the same intensity. (*b*) Profiles of mean rating scores for three synthesized samples with the same fundamental frequency.

more than one perceptual dimension or factor might be related to these scales in contrast to the case for the study of general concepts since the score values for a given voiced sample varied from scale to scale.

The score values for the remaining 4 scales (fast–slow, active–passive, sharp–dull and hot–cold) also revealed complicated profiles for both normal and pathologic voices though the degree of variation from the central line was rather limited. It was interesting to note that on the "hot–cold" scale the values for the normal voices fall mostly in the limited range on the left (hot) side of 0 (Fig. 2), while the scores for the pathologic stimuli cluster on the right (cold) side (Fig. 1, 2, and 3).

2. Synthesized samples

Figure 4 shows the profile for the 9 synthesized vowel samples. When this figure is compared with the profiles of the normal voices in Fig. 3, the following special features may be noticed. (1) All the samples except one are rated as very "clean" on the clean–dirty scale, though the ratings on the other 3 of the 4 initial scales were located close to the center line, as was the case for the normal voiced stimuli. (2) The profiles on the second group of scales are somewhat simpler in shape than those for the normal voices. (3) The profiles on the third group of scales except for the hot–cold scale tend to shift to the left (fast) side. (4) All the scores on the hot–cold scale concentrate on a limited area on the right (cold) side of the center. It may be said that the electrically synthesized vowels are rated to be "cleaner" and "colder" than the normal voices.

Fig. 5*a* shows a profile for the mean rating of the 3 samples that had the same intensity, and Fig. 5*b* illustrates the behavior of the samples which had the same fundamental frequency. It is seen in Fig. 5*a* that the scores shift to the left on the 4 second-group scales (strong–weak, large–small, heavy–light, and hard–soft) and on the "active–passive" scale in accordance with the increase in intensity. The other scales seem to be insensitive to the change in intensity.

The relation between the fundamental frequency and the averaged rating score seems to be somewhat more complicated than that be

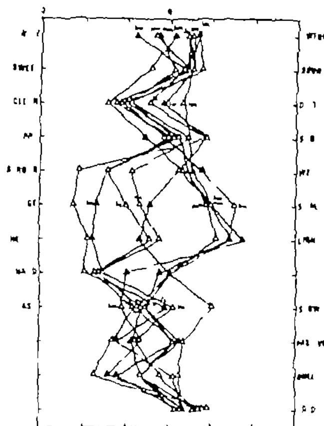


Fig 4 Profiles of mean rating scores for 9 synthesized vowel samples on 1 adjective scales for test 4

by the same 6 listeners for the two occasions was 0 86 Here again even though the cor relation coefficient may not strictly represent the test–retest reliability at any given level of significance it seemed to imply a tolerable replicability

B PROFILES OF THE SAMPLES ON THE SCALES

1 Voiced samples

Figures 1 2 and 3 depict the profiles of the mean rating scores on the adjective scales for tests 1 2 and 3 respectively The response to the normal voice stimuli can be seen in Figs 1 and 2 It is observed in Fig 1 that the scores for the normal subject do not greatly deviate from the central line while most of the pathologic profiles deviate considerably On the initial 4 scales (nice–awful sweet–sour clean–dirty and happy–sad) in particular the scores for the normal voice are all close to 0

This tendency can be seen in Fig 2 as well Although the values for normal voices in Fig. 2 vary considerably on some scales they show little variation from the middle line on the initial 4 scales It is interesting to note that the scores for each pathologic voice on these 4 scales is relatively constant for each voice As a result the profiles of all voices on these scales look almost vertical and parallel to the central 0 line The distance from the mid-line for these pathologic cases however is seen to vary from patient to patient depending upon the nature and degree of the pathology

This fact may indicate that these scales represent the same factor which is of an eval uative nature in the realm of perception of human voice as in the case of other general concepts studied by Osgood et al It was anticipated that there could be certain superior voices which would be rated as very nice very clean and so forth However almost all the normal voices were seen to cluster around the center line on these scales as mentioned above and no superior" rating was observed Similar results were described by Kreul & Hecker (1971) and by Levin et al (1961)

The scores for the 9 patients in test 3 also revealed essentially the same behavior on these 4 scales as shown in Fig 3 The considerable deviation from the central line seen in this figure seems to be attributable to the fact that this group included many advanced or serious cases with respect to the laryngeal status It should be noticed that most of the values were less than 0 i e the data located mainly on the right (awful) side

The scores for the voiced stimuli on the 5th 6th 7th and 8th scales (strong–weak large–small heavy–light and hard–soft) showed a remarkable variation as seen in Figs 1 2 and 3 It is noteworthy that the magnitude of such variation on these scales for the nor mal voices (as it observed in Fig 2) is almost equivalent to that for the pathologic utterances (as is demonstrated in Fig 3) The shapes of profiles for both normal and pathologic voices are quite complicated It was assumed that

Table II *Coordinate values on the dominant dimensions for tests 1 2 and 3*

Dimension	Voice									
a. Test 1	N-1	P 1	P 2	P 3	P-4	P 5				
D-I 1	40	516	121	182	243	317				
D-II-1	−105	0	−38	227	64	386				
D-III-1	40	2	−130	304	−36	1				
b. Test 2	P 1	P-5	N-2	N-3	N-4	N-5	N-6	N 7	N-8	N-9
D-I-2	340	547	−88	124	16	−89	14	107	51	−26
D-II	403	1	105	32	−221	222	250	39	−177	237
D-III-2	2	0	63	141	−201	109	288	158	−166	93
Test 3	P-6	P 7	P-8	P 9	P 10	P 11	P 12	P 13	P 14	P 15
D-I-3	102	312	−6	556	454	−98	236	426	229	370
D-II-3	−188	−101	309	0	−200	356	−75	−238	−169	−70
D-III-3	43	8	−64	1	−129	−1	−151	198	−129	−71
D-IV 3	87	344	66	2	110	−1	75	103	99	179

sions were found for test 3 These dimensions will be referred to as D-I 1 D-I 2 D-I 3 D-II 1 etc., where the last digits 1 2, and 3 correspond to each test, the Roman numerals represent the dimension and the D refers to the dimension extracted by the D-method. Table II (parts *a* *b* and *c*) shows the coordinate values for each analysis. It is observed that in terms of the coordinate values the difference between the two pathologic voices that are common to tests 1 and 2 (P 1 and P 5) remains unchanged

The relationship between the extracted dimensions and the original rating scales was first studied Table III shows the correlation coefficients among the coordinate values on the dominant dimensions and the mean rating scores on the 17 scales. The variability of the extracted dimensions attributable to the difference in object (stimulus) group may be learned from this table since the main differences among tests 1 and 3 were those of stimulus structure

Table IV demonstrates the relationship among the extracted dimensions and the breathy score the rough score and the values of 3 acoustic parameters. The correlation coefficients among the different dimensions themselves are also shown in this table The data for voice P 15 were not included since acoustic analysis was not possible on this sample because of an extreme irregularity in the wave forms.

(*a*) *Test 1* It is observed that dimension D-I 1 is correlated to the breathy score This dimension may be related to evaluating the character of voice especially in terms as "weak" "sad" etc and seems to be related to the loudness impression and also to evaluation The D-III 1 dimension is correlated to the fundamental frequency

(*b*) *Test 2* The dimensions extracted from the data of test seem to be somewhat more complex than those from test 1 Dimension D-I 2 is seen to associate with the APQ and with both the breathy and rough scores. This dimension seems to be of an evaluative character Dimension D-II 2 is connected with such words as heavy" "large" etc. and reversely with the fundamental frequency Dimension D-III 2 is characterized by such words as slow hot etc. and is also inversely related to the fundamental frequency

tween the intensity and the mean score as is seen in Fig 5b The scores shift to the left side with the increase in fundamental frequency on the initial 4 scales (which seemed to be of an evaluative nature) The same holds true on the "fast–slow and sharp–dull" scales among the third group of scales On the second group of scales on the contrary the high pitched (300 Hz) or the medium pitched (205 Hz) samples are seen to deviate to the right side though these two kinds of samples did not reveal different profiles on this group of scales The low pitched stimuli (100 Hz) were apparently judged to be stronger larger and heavier than other samples The hot–cold scale seemed to be related neither to intensity nor to fundamental frequency

The results of test 5 in which 9 normal and 15 pathologic voices were rated on Japanese scales by Japanese laryngologists were found to be in very good agreement with the results shown in the figures for English scales As discussed later in a separate section further analyses confirmed this similarity and since they would therefore be redundant the results are not shown separately here

C RATING OF BREATHINESS AND ROUGHNESS

It is apparent that there exists considerable interaction between perceptions of breathiness and roughness judging from the regression in Fig 6 and from the significant correlation coefficient between them ($r=0.47$) It should be mentioned however that there are certain voices which were judged to be very rough yet not at all breathy It is evident that the concepts of breathiness and roughness involve certain different semantic contents though it seems to be clear that neither of these two concepts can be an entirely independent factor in the perceptual space

It should also be noticed that most normal voices were judged to be slightly rough or breathy No evident distinction could be observed between the normal and the pathologic voices in terms of these ratings The correlation coefficient between the two judges for these rating scores was 0 77 which was significant though this value was not considered to be high

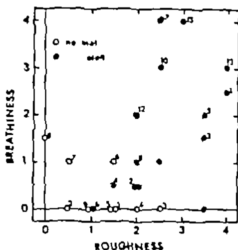


Fig 6 Scatter diagram of 24 voiced samples on the breathy–rough plane Each numeral attached to the circles indicates the sample number (see Table I)

D RESULTS OF FACTOR ANALYSIS

Section 1 D-method of factoring

The above mentioned rating scores were subjected to factor analyses The D-method of factoring yielded a series of coordinate values on the extracted dimensions for each stimulus The following criterion was adopted to determine whether or not a resulting dimension is dominant On each dimension extracted by this method the difference between the maximum and minimum was calculated For the ith dimension this value was called the range R_i If a dimension had an R_i value that was larger than 50% of the largest R_i (R_{max}) this dimension was defined to be dominant In most cases however the determination of the dominant dimensions was not difficult since the absolute coordinate values decreased rather sharply where dominant dimensions no longer existed

1 Voiced samples

Three dominant dimensions were extracted for both tests 1 and 2 and 4 dominant dimen

Table II *Coordinate values on the dominant dimensions for tests 1 2 and 3*

Dimension	Voice									
Test 1										
	N-1	P 1	P	P 3	P-4	P-5				
D-I-1	40	516	121	182	43	317				
D-II-1	−105	0	−38	227	64	386				
D-III 1	40	2	−130	304	−36	1				
b Test 2										
	P 1	P 5	N 2	N 3	N-4	N-5	N-6	N-7	N-8	N-9
D-I-	340	547	−88	124	16	−89	14	187	51	−26
D-II-2	403	1	105	32	−221	232	250	39	−177	237
D-III-2	2	6	63	141	−201	109	288	138	−166	93
Test 3										
	P-6	P 7	P-8	P-9	P 10	P 11	P 12	P-13	P 14	P 15
D-I-3	102	312	−6	336	454	−98	36	426	229	330
D-II 3	−108	−101	309	0	−200	356	−75	−238	−169	−70
D-III-3	43	0	−64	1	−129	−1	−151	198	−129	−71
D-IV 3	87	244	66	2	110	−1	75	103	99	179

sions were found for test 3 These dimensions will be referred to as D-I 1 D-I ,, D-I 3 D-II 1 etc. where the last digits 1 2, and 3 correspond to each test, the Roman numerals represent the dimension, and the D refers to the dimension extracted by the D-method Table II (parts *a* *b* and *c*) shows the coordinate values for each analysis It is observed that in terms of the coordinate values the difference between the two pathologic voices that are common to tests 1 and 2 (P 1 and P 5) remains unchanged

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Table IV demonstrates the relationship among the extracted dimensions and the breathy score the rough score and the values of 3 acoustic parameters. The correlation coefficients among the different dimensions themselves are also shown in this table The data for voice P 15 were not included since acoustic analysis was not possible on this sample because of an extreme irregularity in the wave forms.

(*a*) *Test 1* It is observed that dimension D-I 1 is correlated to the breathy score This dimension may be related to evaluating the character of voice especially in terms as "weak" "sad" etc. and seems to be related to the loudness impression and also to evaluation The D-III 1 dimension is correlated to the fundamental frequency

(*b*) *Test 2* The dimensions extracted from the data of test 2 seem to be somewhat more complex than those from test 1 Dimension D-I 2 is seen to associate with the APQ and with both the breathy and rough scores. This dimension seems to be of an evaluative character Dimension D-II 2 is connected with such words as heavy" large etc and reversely with the fundamental frequency Dimension D-III 2 is characterized by such words as slow" hot" etc and is also inversely related to the fundamental frequency

Table III *Correlation coefficients between the coordinate values on the dominant dimensions and the mean rating scores on the adjective scales*

Dimension	Scales Nice-awful	Sweet-sour	Clean-dirty	Happy-sad	Strong-weak	Large-small	Heavy-light	Hard-soft	Fast-slow
D-I 1	−0 75	−0 94	−0 75	−0 67	−0 1	0.37	0.87*	0.14	−0.42
D-II 1	−0 79*	−0 48	−0 81	−0.85	−0 98	−0.37	−0.14	−0.09	−0 20
D-III 1	−0 4	−0 1	−0.37	−0 47	−0 41	−0.9?	−0.31	0.79*	0.81
D-I	−0 9	−0 68	−0 85	−0 76	−0 77	−0.40	−0._5	0.03	−0 03
D-II	−0 33	−0 65	−0.50	−0.54	0.57	0.85	0.93	0 65	−0.78
D-III	0 0?	−0.33	−0.?0	−0 45	0 60*	0 82	0.78	−0 1	−0 9?*
D-I 3	−0 91	−0 99*	−0 95	−0 91	0 05	0.7?	0.81	0.34	−0 73**
D-II 3	0 54	0 68	0 72	0 84**	−0 67	−0 94	−0 94	0 06	0.87*
D-III 3	−0.05	−0 15	−0.07	0 09	0 46	0.35	0.31	0 73	0 57
D-IV 3	−0 67	−0.3	−0.56	−0 34	0 12	0.05	0.09	−0.52	0.85

*=significant at the 5% level
**=significant at the 1% level

It is noteworthy that there is an interaction between dimensions D-II 2 and D-III 2 ($r = 0\ 64$)

(c) *Test 3* Dimension D-I 3 from test 3 is seen to correlate with such terms as "sour" "dirty" etc and with the APQ the rough score the FPQ and reversely with the FF It may be said therefore that D-I 3 is related mainly to the evaluation of the quality judging from the words with which it is associated

Dimension D-II 3 on the other hand is associated positively with the FF This dimension apparently is connected with pitch sensation D-III 3 has little to do with the acoustic parameters measured Dimension D-IV 3 is associated with the breathy score

(d) *Analysis on all voiced samples* Figure 7 illustrates 3 two-dimensional representations of the coordinate values for the 3 tests al-

Table IV *Correlation coefficients between the coordinate values on the dominant dimensions and the breathy score the rough score and the 3 acoustic parameter values for the tests 1 2 and 3*

	Breathy score	Rough score	FF	FPQ	APQ	D-II 1	D-III 1	
D-I 1	0.88	0 74	0 1	0 44	0.60	0.29	−0.07	
D-II 1	0 56	0.56	0.43	0.16	0 56		0 38	
D-III 1	0. 4	0 41	0 81	0 7?	0.58			
						D-II 2	D-III	
D-I	0 79*	0 71	0.16	0 41	0 88	0 01	0 1	
D-II 2	0 18	0.3_	−0 67*	0.36	0 77		0 64	
D-III	−0 15	0 04	−0.88	−0.1	−0 13			
						D-II 3	D-III 3	D-IV 3
D-I 3	0.39	0.7?	−0.67	0 68	0 95	−0.68	0 33	0 10
D-II 3	−0.39	−0 25	0.94	−0 05	−0.51		0 21	−0.11
D-III 3	−0.06	0 39	−0 19	0 09	0 14			−0 18
D-IV 3	0.89*	0.42	−0._1	−0 00	0.37			

*=significant at the 5% level.
**=significant at the 1% level.

Active–passive	Sharp–dull	Hot–cold
0.38	−0.60	0.23
−0.75	0.15	−0.71
[illegible]	0.83	−0.71
−0.74**	−0.28	−0.22
0.27	−0.72	0.37
−0.17	−0.78**	0.88**
−0.34	−0.63	−0.37
0.52	0.87**	−0.12
0.70*	0.33	−0.19
−0.01	−0.42	0.24

together When the factor analysis was made *on the total data of 24 voiced stimuli* 4 dominant dimensions were extracted For voices P 1 and P 5 the rating scores in test 1 were adopted. These dimensions will be referred to as D-I NP D-II NP etc. where N stands for "normal" and P for pathologic It should be mentioned however that some *mathematical* requirements for the statistical model may not be fulfilled for the analysis of such pooled data. The homogeneity of the data, for example cannot be guaranteed. The *results of* such an analysis therefore have to be *carefully* interpreted and should not be widely generalized

Table V shows the correlation matrix among the breathy and the rough scores the fundamental frequencies the frequency perturbation quotients, the amplitude perturbation quotients and the coordinate values on the D-I NP D-II NP D-III NP and D-IV NP dimensions for the 9 normal and 14 pathologic voices. P 15 was not included Table VI gives a set of correlation coefficients between the mean rating scores on the 1? scales and the coordinate values on the 4 perceptual dimensions for the total voiced samples.

It is understood from Tables V and VI that D-I NP is characterized mainly by such terms as awful" "sour" "dirty" etc and is correlated to both of the breathy and rough scores as well as to both of the FPQ and APQ This dimension evidently is *of* an *evaluative* nature D-II NP is associated with such terms as "*large*" heavy etc It seems reasonable to relate this dimension to loudness sensation *D-I'I NP is connected with* such terms as *"sharp" "fast etc and is positively* cor related to the FF This dimension is apparently *related to pitch* sensation.

D-IV NP is correlated with the breathy score *and with the APQ* and seems to be associated with the perception of breathiness It *may be noted that* the voices which reveal *high* values on this dimension i.e. P 1 P 5 and P *15* are from the patients *with* unilateral paralysis, and *P 7* is a very breathy voice from a case having undergone *partial laryngectomy*



Fig 7 Scatter diagram of ... voiced samples on the ... [illegible]

Table III *Correlation coefficients between the coordinate values on the dominant dimensions a the mean rating scores on the adjective scales*

Dimension	Scales: Nice–awful	Sweet–sour	Clean–dirty	Happy–sad	Strong–weak	Large–small	Heavy–light	Hard–soft	Fast–slow
D-I 1	−0 75	−0 94	−0 75	−0 67	−0 1	0.37	0.87	0 14	−0 42
D-II 1	*−0 79**	*−0 48*	*−0 81*	*−0 85*	*−0 98*	*−0.37*	*−0 14*	−0 09	−0 70
D-III 1	−0 4?	−0 21	−0 37	−0 47	−0 41	−0.92	−0.31	0 79*	0 81
D-I 2	*−0 9*	−0 68	−0 85	−0 76	−0 77	−0 40	−0.‿5	0 03	−0.03
D-II	−0 33	−0 65	−0 50	−0 54	0 57	0 85	0 93	0 65	−0 78
D-III ?	0 02	−0.33	−0 70	−0 45	0 60	0 82	0 78	−0 1	−0.9?
D-I 3	−0 91	−0 99*	−0 95	−0.91	0.05	0 72	*0 81*	*0.34*	−0 75
D-II 3	0.54	0 68	0 72	0 84	−0 67*	−0 94	−0.94	0 06	0 87*
D-III 3	−0 05	−0 15	−0 07	0 09	0 46	0.35	0.31	0.73	0 17
D-IV 3	*−0 67*	*−0.3*	*−0 56*	*−0.34*	*0 12*	*0 05*	*0 09*	*−0.3?*	*0 01*

*=significant at the 5% level
=significant at the 1% level

It is noteworthy that there is an interaction be tween dimensions *D-II 2 and D-III 2 (r=0 64)*

(c) *Test 3* Dimension D-I 3 from test 3 is seen to correlate with such terms as sour dirty etc and with the *APQ* the rough score the FPQ and reversely with the *FF* It may be said therefore that D-I 3 is related mainly to the evaluation of the quality judging from the words with which it is associated

Dimension D-II 3 on the other hand is as *sociated positively with the FF This dimen* sion apparently is connected with pitch sensa *tion D-III 3 has little to do with the acoustic* parameters measured Dimension D-IV 3 is associated with the breathy score

(d) Analysis on all voiced samples Figure 7 illustrates 3 two-dimensional representations of the coordinate values for the 3 tests al

Table IV *Correlation coefficients between the coordinate values on the dominant dimensions and the breathy score the rough score and the 3 acoustic parameter values for the tests 1 2 and 3*

	Breathy score	Rough score	FF	FPQ	APQ	D-II 1	D-III 1	
D-I 1	0 88	0 74	0 12	0 44	0.60	0.79	−0 07	
D-II 1	0 56	0.56	0 43	0 16	0.56		0.38	
D-III 1	0 4	0 41	0 81	0.7?	0.58			
						D-II	D-III 2	
D-I 2	*0 79*	*0 71*	0 16	0 41	0 88	0 01	−0 12	
D-II	0 18	0 3	−0 67	0.56	0 27		0 64	
D-III 2	*−0 15*	*0 04*	−0 88	−0.1	−0 13			
						D-II 3	D-III 3	D-IV 3
D-I 3	*0.39*	*0 7?*	*−0 67*	*0 68*	0 95	−0.68	0 33	0 10
D-II 3	−0.39	−0 ‿5	0.94	−0 05	−0.51		−0 1	−0.11
D-III 3	−0 00	0 39	−0 19	0.09	0 14			−0 18
D-IV 3	0 69*	*0.4*	*−0 21*	*−0.00*	*0.37*			

*=significant at the 5% level
=significant at the 1% level*

Table VII *Coordinate values on 3 dimensions for test 4*

h high, l=low strong, w weak, m=medium

	hm	lm	hs	mm	hw	ms	lw	mw	ls
D-I-S	346	−65	448	−102	−175	205	60	−116	276
D-II S	25	340	0	175	192	107	−87	158	238
D-III-S	−18	2	3	−4	−6	134	0	17	29

same fundamental frequency It is seen in this figure that the first dimension D-I S is related to the intensity i e. the "stronger samples consistently have larger coordinate values than the "weaker" samples and vice versa. Similarly D-II S is apparently related to the fundamental frequency It is presumed that the dimension associated with evaluation did not reveal itself as a dominant dimension because the quality of the synthesized stimuli was controlled to be the same except for the fundamental frequency and the intensity This may also be predicted from the profiles of these samples on the first group of adjective scales

3 *Additional analysis*

The factor analysis was also carried out on the combined data of the normal and the pathologic voices together with the synthesized vowel samples as a reference Because of a space limitation in the computer used for the analyses however the data of only 4 of the 9 normal voices (N-4 to N 7) and 6 of the synthesized samples (three high s and three low"s) were added to those of the 15 pathologic voices Four dominant dimensions were extracted. Figure 9 demonstrates the location of the samples on the I II I III and I IV planes. These dimensions are referred to as D-I NPS D-II NPS etc. It is apparent that the direction of the extracted dimensions varies considerably by adding or altering the data as can be seen by comparing the location of each point in Fig. 7 or in Fig. 8 with that in Fig. 9

Section 2. Maximum likelihood method with varimax rotation

1 *On English scales*

The mean rating scores on the 12 English scales for each voice were intercorrelated with the 3 acoustic parameters (P 15 was omitted

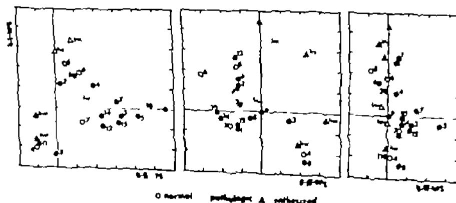


Fig 9 Scatter diagrams of 4 normal and 9 pathologic voiced samples together with 6 synthesized vowel samples on the I-II, I-III and I-IV planes.

Table V *Correlation matrix of breathy and rough scores fundamental frequencies (FF) frequency perturbation quotients (FPQ) amplitude perturbation quotients (APQ) and the coordinate values on dimensions D-I NP D-II NP D-III NP and D-IV NP*

	Rough	FF	FPQ	APQ	D-I NP	D-II NP	D-III NP	D-IV NP
Breathy	0 47	−0 06	0.18	0.56	0.58	0 76	0 00	0.57*
Rough		0 13	0.55	0 77	0 77	0.3	0.13	0.35
FF			0.09	−0 13	−0.29	−0 77	0.83	0.16
FPQ				0 77	0 67*	0 05	0.13	0 08
APQ					0 86	0.26	0 00	0.46
D-I NP						0 4	−0.30	0.43
D-II NP							−0 70*	−0 25
D-III NP								0 10

n = 3
*=significant at the 5% level
**=significant at the 1% level

The breathy score in Table V reveals correlation with the APQ while the rough score is connected with both the FPQ and APQ The results agree with those of Wendahl (1963 1966*a* 1966*b*) who observed that rapid variations in fundamental frequency (jitter) and amplitude variations (shimmer) of synthesized stimuli yield perceptive roughness or harshness

Table VI *Correlation coefficients between the rating scores on the adjective scales and the coordinate values on the 4 dimensions for total voiced samples*

	D-I NP	D-II NP	D-III NP	D-IV NP
Nice–awful	−0 93	−0.28	0 07	−0.64
Sweet–sour	−0 94	−0.55	0 33	−0 28
Clean–dirty	−0 97*	−0 4	0 79	−0 53
Happy–sad	−0 90	−0 48	0.48	−0 57
Strong–weak	−0 20	0 77*	−0 51	−0.59
Large–small	0 39	0.91	−0 76	−0 23
Heavy–light	0 99*	0 93	−0 77*	−0.70
Hard–soft	0 3	0.28	0.17	−0 45
Fast–slow	−0 49*	−0 61	0.9**	−0 04
Active–passive	−0 34	0 18	0 4	−0 59*
Sharp–dull	−0.45	−0 71	0 84	−0 70
Hot–cold	−0.3	0.53	−0.54	−0.35

n = 4
*=significant at the 5% level
**=significant at the 1% level

2 *Synthesized samples*

Two dominant dimensions were extracted and denoted D-I S and D-II S (S indicates "synthesized") from the data on synthesized vowel samples Table VII shows the coordinate values for each stimulus on the extracted dimensions and Fig 8 shows the positions of the samples on the I II plane The broken lines in this figure connect the samples having the

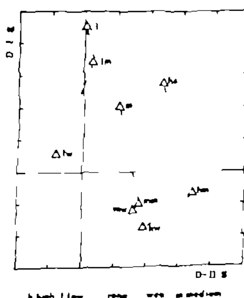


Fig 8 Scatter diagram of 9 synthesized vowel samples on the I II plane of dimensions

Table IX. *Rotated factor loadings (English)*

Scales	Loadings				Commonality
	F-I	F-II	F-III	F-IV	
Nice-awful	0.99*	0.08	0.00	0.13	0.99
Sweet-sour	0.84	0.43	0.00	−0.15	0.91
Clean-dirty	0.9?*	0.31	−0.02	0.06	0.94
Happy-sad	0.47	0.72*	0.29	0.24	0.88
Strong-weak	0.16	−0.?4	0.91	0.25	0.98
Large-small	0.36	−0.58*	0.60*	0.27	0.89
Heavy-light	−0.36	−0.82*	0.36	0.23	0.98
Hard-soft	−0.36	0.92	0.18	0.82	0.83
Fast-slow	0.02	0.87*	−0.02	0.08	0.76
Active-passive	0.17	0.20	0.25	0.44	0.3?
Sharp-dull	0.25	0.79*	−0.16	0.46	0.93
Hot-cold	0.45	−0.52*	0.36	−0.22	0.66
FF	0.05	0.83	−0.23	0.05	0.73
FPQ	−0.69*	0.03	−0.20	0.37	0.65
APQ	−0.91	−0.04	0.01	0.06	0.84
Variance accounted for (%)	31.8	28.4	11.6	10.4	82.2

* significant

nevertheless, are seen to correlate with such major characteristics as evaluation loudness and pitch though which dimension cor responds to which character has to be ex amined each time

The 4 dominant factors extracted by Isshiki et al (1969) with the use of the same proce dure as ours should correspond to the dimensions discussed above. Although they named their factors "rough" (R) "breathy" (B) asthenic" (A) and "degree" (D) respec tively such a labeling has no tenable basis and is misleading. Further the orientation of such factors will vary for different sets of stimuli

Table X *Rotated factor loadings (Japanese)*

Scales*	Loadings				Commonality
	F-I	F-II	F-III	F-IV	
Nice-awful	0.87*	0.28	0.31	0.22	0.98
Sweet-sour	0.93	−0.08	0.?4	−0.11	0.93
Clean-dirty	0.87*	0.17	0.33	0.28	0.97
Happy-sad	0.87*	0.29	0.31	0.19	0.96
Strong-weak	0.20	0.94	−0.02	−0.09	0.94
Large-small	0.03	0.92*	−0.32	0.2?	0.99
Heavy-light	−0.46	0.15	−0.80*	0.18	0.91
Hard-soft	−0.80*	0.49	0.1	0.11	0.90
Fast-slow	0.48	0.38	0.77*	0.12	0.98
Active-passive	0.41	0.73	0.38	0.05	0.88
Sharp-dull	0.58	0.26	0.66	0.37	0.98
Hot-cold	−0.09	−0.06	−0.44	−0.84	0.9?
FF	0.01	0.17	0.77*	0.18	0.66
FPQ	−0.60*	−0.37	−0.31	0.12	0.46
APQ	−0.70*	−0.40	−0.13	−0.28	0.78
Variance accounted for (%)	37.4	1.6	20.8	8.5	88.1

a Original English scales are shown here instead of Japanese scales.
* significant

Table VIII *Correlation matrix for 12 adjective scales and 3 acoustic parameters*

	Sweet–sour	Clean–dirty	Happy–sad	Strong–weak	Large–small	Heavy–light	Hard–soft	Fast–slow	Active–passive	Sharp–dull	Hot–cold	FF	FPQ	APQ
Nice–awful	0 85	0 94	0.56	0 17	−0.36	−0 39	−0 25	0 10	0_4	0 37	0.38	0.1	−0 63	0.90
Sweet–sour		0 89	0 64	−0 01	−0.57	−0 69	−0 4	0 41	0 15	0 48	0.16	0.34	−0 64	−0.78
Clean–dirty			0 63	0 07	−0.53	−0.58	−0 27	0 33	0 31	0.50	0 26	0.79	−0.57	0.83
Happy–sad				0 22	−0 34	−0 60	0.09	0 60	0.35	0.76	−0 1	0.61	−0.22	0.44
Strong–weak					0 70	0.53	0.31	−0.21	0 32	−0.19	0.48	−0.39	−0.20	−0.11
Large–small						0 88	0 45	−0 47	−0 04	−0.52	0_4	−0 62	0.17	0.36
Heavy–light							0.36	−0 70	−0 01	−0 68	0.36	−0 77	0_3	0.37
Hard–soft								0 09	0 41	0.26	−0.3	−0.04	0.54	0 43
Fast slow									0 34	0 76	−0 46	0 69	−0.10	−0 04
Active–passive										0 35	0 13	0.18	−0.01	−0.17
Sharp–dull											−0 49	0.75	0 05	−0 26
Hot–cold												−0 44	−0 41	0.37
FF													0.09	−0 13
FPQ														0.7?

for the reason mentioned above) Table VIII displays the 15×15 correlation matrix This matrix was then subjected to the Lawley s maximum likelihood analysis and was rotated by the varimax method in order to obtain a *simple orthogonal structure* Table IX represents the results

2 *On Japanese scales*

The same analysis procedure was repeated on the data obtained with the use of Japanese scales and Japanese listeners as in the case of English scales The results are given in Table X

Discussion

A DIMENSIONS EXTRACTED BY D-METHOD FACTORING

The profiles of the data from tests 1 2 and 3 reveal particularly when they are compared with those from test 4 that certain acoustic features such as the fundamental frequency and intensity of the stimuli do affect the perceptual judgments on the adjective scales adopted A considerable shift on the scales observed both in normal and pathologic samples seems to be mostly attributable to the differences in such basic features rather than to some particular pathologic characteristics of the stimulus voices It is quite probable that certain combinations of such basic characters as fundamental frequency or intensity are playing some complicated roles in judging the voice quality

It is also noteworthy that there is a certain cue which is evidently associated with the evaluation of the degree of voice abnormality The factor represented by the first 4 pairs of words for example reveals appreciable dispersions only for the pathologic stimuli This perceptual mechanism obviously works when the stimuli include some pathologic utterances

The D-method of factoring typically reveals 3 or 4 dominant dimensions associated with evaluation loudness and pitch as mentioned above Since the orientation of the dimensions with this analysis method is determined by the particular set of data under analysis any change in the data structure will result in an alteration of the direction of the dimensions This is evidently recognized from the results of tests 1 2 and 3 The resulting dimensions

Table IX. *Rotated factor loadings (English)*

Scales	Loadings F-I	F-II	F-III	F-IV	Commonality
Nice-awful	0.99*	0.08	0.00	0.13	0.99
Sweet-sour	0.84	0.43	0.00	−0.15	0.91
Clean-dirty	0.92*	0.31	−0.02	0.06	0.94
Happy-sad	0.47	0.72*	0.29	0.24	0.88
Strong-weak	0.16	−0.24	0.91	0.25	0.98
Large-small	−0.36	−0.58*	0.60*	0.27	0.89
Heavy-light	−0.36	−0.82	0.36	0.23	0.98
Hard-soft	−0.96	0.02	0.18	0.02	0.83
Fast-slow	0.02	0.87*	−0.02	0.06	0.76
Active-passive	0.17	0.20	0.25	0.44	0.5
Sharp-dull	0.25	0.79*	−0.16	0.46	0.93
Hot-cold	0.45	−0.57	0.36	−0.22	0.66
FF	0.05	0.83	−0.23	0.05	0.73
FPQ	−0.69*	0.03	−0.20	0.37	0.65
APQ	−0.91	−0.04	0.01	0.06	0.84
Variance accounted for (%)	31.8	28.4	11.6	10.4	82.2

*significant.

nevertheless, are seen to correlate with such major characteristics as evaluation loudness and pitch, though which dimension corresponds to which character has to be examined each time.

The 4 dominant factors extracted by Isshiki et al. (1969) with the use of the same procedure as ours should correspond to the dimensions discussed above. Although they name their factors "rough" (R) breathy" (B "asthenic" (A) and "degree (D) respectively such a labeling has no tenable basis an is misleading. Further the orientation of suc factors will vary for different sets of stimul

Table X. *Rotated factor loadings (Japanese)*

Scales*	Loadings F-I	F-II	F-III	F-IV	Commonality
Nice-awful	0.87*	0.28	0.31	0.22	0.98
Sweet-sour	0.93	−0.08	0.24	−0.11	0.93
Clean-dirty	0.87	0.17	0.33	0.28	0.97
Happy-sad	0.87*	0.28	0.31	0.19	0.96
Strong-weak	0.70	0.94*	−0.02	−0.09	0.94
Large-small	0.03	0.92*	−0.32	0.22	0.99
Heavy-light	0.46	0.15	−0.80*	0.18	0.91
Hard-soft	−0.80*	0.49	0.12	0.11	0.90
Fast-slow	0.48	0.38	0.77*	0.12	0.98
Active-passive	0.41	0.75	0.38	0.05	0.88
Sharp-dull	0.98*	0.76	0.66	0.37	0.98
Hot-cold	−0.09	−0.06	−0.44	−0.84*	0.97
FF	0.01	−0.17	0.77*	0.18	0.66
FPQ	−0.60*	−0.77	−0.11	0.17	0.46
APQ	0.70*	−0.40	−0.15	0.28	0.76
Variance accounted for (%)	37.4	1.6	20.8	8.5	88.1

Original English scales are shown here instead of Japanese scales.
*significant.

The classification of hoarseness based upon such undefined factors has to be inherently quite arbitrary and subjective

It is seen in Fig 9 that there exist several clusters of pathologic voices in terms of the D-I NPS dimension (which is highly correlated with D-II NP and is associated with loudness sensation) For example P 1 and P 13 which have similar coordinate values on the ordinate are the voices of pre and post-operative laryngeal cancer respectively The voices of patients with unilateral paralysis i e P 3 P 5 and P 15 have similar coordinate values on this axis These two groups are well separated on this dimension On the other hand on D-III NPS (which is highly correlated with D-III NP and is connected with pitch sensation) most of the pathologic voices have similar coordinate values on the low pitched side It seems to be reasonable therefore to suppose that certain combinations of the perceptual dimensions corresponding to pitch loudness or evaluation are to a considerable extent related to the auditory categorization of laryngeal diseases as mentioned earlier in this section

B THE FACTORS EXTRACTED BY THE MAXIMUM LIKELIHOOD METHOD

It is observed in Table IX that F I (the first factor) extracted by Lawley s Maximum Likelihood Method is characterized by such terms as "awful "sour and dirty and is correlated reversely with the FPQ and APQ This factor seems to be of evaluative nature as in the case of the D-I NP extracted by the D-method F II reveals relationship to fast light" "sharp and some other terms and is seen to correlate with fundamental frequency This factor evidently is connected with pitch sensation F III demonstrates significant coefficients with "strong" and "large" and is apparently related to loudness sensation F IV is associated only with "hard" at one extreme

It is interesting to note that some of these

Table XI *Correlation matrix of the 4 factors extracted by the maximum likelihood method*

	F-II	F-III	F IV
F I	−0 00	0 00	0.01
F II		−0 02	0.03
F-III			0.00

factors showed evident relationships with certain acoustic measures studied A very high correlation value (0 91) between the APQ and F I (which seems to be evaluative) in Table IX for example seems to be particularly noteworthy This figure implies that over 80% of the variances associated with this axis can be accounted for by the APQ In other words the APQ may have been a tangible acoustic correlate to this dimension This tendency is also recognized from the results of the D-method where the correlation coefficient between the D-I NP and the APQ reached 0 86 which was the highest value in Table V

Similarly F II revealed a high correlation coefficient (0 83) with the fundamental frequency The same held true with the relationship between the D-III NP and the FF (0 83) Here again most (69%) of the variances could be accounted for by this correlate

Since the intensities of the stimuli were adjusted to be the same except for the synthesized samples the effects of the intensity upon the factors have to be examined in directly from the results of synthesized stimuli It seems rather apparent nevertheless that F III is strongly related to the intensity though the judgment of the intensity (or "loudness in a psychological sense) would have been based more on some other features such as the sensation of vocal effort than on the actual intensities of the stimuli

The acoustic correlate to F IV has not become clear from the present data. D-IV NP however was seen to correlate with the breathy score and with the APQ It is believed that the factors such as the F IV or the D-IV NP should not be neglected when minor per

ceptual differences among pathological voices are to be studied, even if a definite acoustic correlate has not yet been explicated.

C. COMPARISON OF THE RESULTS OBTAINED BY DIFFERENT FACTOR ANALYTIC METHODS

There exists an apparent similarity between the result of the D-method and that of Lawley's method with varimax rotation. The first 3 dimensions from the D-method and the initial 3 factors extracted by the Maximum Likelihood Method are quite alike. They related to "evaluation", "loudness" and "pitch" respectively. A major difference between the two kinds of results may be the fact that the dimensions extracted by the D-method are not necessarily independent from each other as shown in Tables IV and V, while the factors extracted by the Maximum Likelihood Method are quite independent as shown in Table XI. For example, the D-II NP (which is related to loudness) was correlated with the D-III NP (which is related to pitch) and with fundamental frequency. No significant correlation was found, on the other hand, between the F III (associated with loudness) and the F II (connected with pitch).

This discrepancy between the two methods may be understandable from the fact that the D-method always extracts the dimensions orthogonal to each other, and no rotation of the dimensions was made to find a better fit to the underlying perceptual dimensionality which may not be necessarily of orthogonal structure. This particular feature of the D-method of factoring should be kept in mind when an interpretation of the results of an analysis with this method is attempted.

D. COMPARISON OF THE DATA OF ENGLISH SCALES AND THOSE OF JAPANESE SCALES

By comparing the results in Table IX with those in Table X, the effect of language environments upon the same set of voice stimuli may be studied. Here again, the nature of the first three factors are very similar, even though the order of F II and F III is reversed. In other words, even though the judges and the language environments were different, a similar result was obtained for the same voice samples as far as the first three factors are concerned. This fact may indicate that, even if there exist subtle differences in meaning between the corresponding scales in Japanese and in English, the perceptive impressions on the same stimuli remain much the same in a relative sense. That is, the perceptual space for the voice quality may not be appreciably affected by the intercultural differences.

E. SOME ADDITIONAL COMMENTS

Although not much emphasis was placed on this point in the present study, the question of the number of dominant dimensions for different sets of stimuli seems to be quite interesting. Our results on the synthesized vowels strongly suggest that for certain stimuli the perceptual dimensions may be less in number than on some other occasions. It is likely, for example, that the dimensions required for the perception of normal voices are only three and that such a three-dimensional space forms a sort of subspace in a more complicated perceptual space that also includes various different pathological voices.

It should be mentioned also that the voiced samples used in the present study were merely some short segments excerpted from the steady-state portions of sustained vowels, which contained neither the vowel initiations nor the terminations. The initial and the terminal parts of the voice may carry abundant information not contained in the steady states. Also, the intensities of the voice stimuli were adjusted to be the same in this study. There should be an apparent variation in the overall intensity for different patients. Further, an abrupt transient occasionally observed, such

The classification of hoarseness based upon such undefined factors has to be inherently quite arbitrary and subjective

It is seen in Fig 9 that there exist several clusters of pathologic voices in terms of the D-I NPS dimension (which is highly correlated with D-II NP and is associated with loudness sensation) For example P 1 and P 13 which have similar coordinate values on the ordinate are the voices of pre and post-operative laryngeal cancer respectively The voices of patients with unilateral paralysis i e P 3 P 5 and P 15 have similar coordinate values on this axis These two groups are well separated on this dimension On the other hand on D-III NPS (which is highly correlated with D-III NP and is connected with pitch sensation) most of the pathologic voices have similar coordinate values on the low pitched side It seems to be reasonable therefore to suppose that certain combinations of the perceptual dimensions corresponding to pitch loudness or evaluation are to a considerable extent related to the auditory categorization of laryngeal diseases as mentioned earlier in this section

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It is observed in Table IX that F I (the first factor) extracted by Lawley s Maximum Likelihood Method is characterized by such terms as "awful sour and dirty and is correlated reversely with the FPQ and APQ This factor seems to be of evaluative nature as in the case of the D-I NP extracted by the D-method F II reveals relationship to "fast" light sharp and some other terms and is seen to correlate with fundamental frequency This factor evidently is connected with pitch sensation F III demonstrates significant coefficients with "strong and large" and is apparently related to loudness sensation F IV is associated only with hard at one extreme

It is interesting to note that some of these

Table XI *Correlation matrix of the 4 factors extracted by the maximum likelihood method*

	F II	F III	F-IV
F I	−0 00	0.00	0 01
F II		−0 02	0 03
F III			0.00

factors showed evident relationships with certain acoustic measures studied A very high correlation value (0 91) between the APQ and F I (which seems to be evaluative) in Table IX for example seems to be particularly noteworthy This figure implies that over 80% of the variances associated with this axis can be accounted for by the APQ In other words the APQ may have been a tangible acoustic correlate to this dimension This tendency is also recognized from the results of the D-method where the correlation coefficient between the D-I NP and the APQ reached 0 86 which was the highest value in Table V

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Since the intensities of the stimuli were adjusted to be the same except for the synthesized samples the effects of the intensity upon the factors have to be examined in directly from the results of synthesized stimuli It seems rather apparent nevertheless that F III is strongly related to the intensity though the judgment of the intensity (or "loudness in a psychological sense) would have been based more on some other features such as the sensation of vocal effort than on the actual intensities of the stimuli

The acoustic correlate to F IV has not become clear from the present data. D-IV NP however was seen to correlate with the breathy score and with the APQ It is believed that the factors such as the F IV or the D-IV NP should not be neglected when minor per

war mit der Stärke der dritte mit der Grundfrequenz der Reizmittel verbunden. Ausser den drei vorherrschenden Faktoren stellten sich auch einige unbedeutendere Faktoren bei der Unterscheidung pathologischer Stimmen als wichtig heraus.

Acknowledgments

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as a voice break often gives an *important* clue to the laryngologist There seem to be many acoustic and perceptual characteristics which remain to be studied

F CONCLUDING REMARKS

It seems justifiable to mention that the perceptual space for voice quality does have a multi-dimensional structure There seem to be 4 dominant dimensions corresponding to *amplitude perturbation to fundamental pitch to* intensity and to some undetermined acoustic *feature respectively though the exact direction observed for each dimension depends* upon the set of auditory stimuli given It was suggested that the perception of certain types of voices may be based on a simpler space *with a smaller number of dimensions forming a kind of subspace within the entire 4-dimen*sional space of auditory perceptions Two different methods of factor analysis revealed essentially the same result as stated above. It was also *suggested that the perceptual space* for voice quality is not remarkably affected by different language environments

Summary

Perceptual criteria for classifying pathologic voices in comparison with normal voices were studied with the use of the semantic dif*ferential technique using 12 pairs of polar* opposite adjectives The factors extracted from the data by means of the D-method and of the maximum likelihood method were correlated to fundamental frequency a frequency *perturbation quotient and an amplitude per*turbation quotient The utterances produced by 9 normal and 15 pathologic subjects together with 9 synthesized vowel samples were investigated The first factor was related to evaluation of voice quality and was also close*ly related to the amplitude perturbation.* The second and the third factors were associated with intensity and fundamental frequency of the stimuli respectively Some minor factors other than the three dominant factors were *also supposed to be relevant to the distinction* of pathologic voices

Zusammenfassung

Wahrnehmbare Kriterien zum Einordnen von pathologischen Stimmen im Vergleich zu normalen Stimmen wurden unter Gebrauch der semantischen Unterscheidungsmethode *unter*sucht die zwölf Paare polar entgegengesetzter *Adjektive verwendete* Die aus den Resultaten vermittels der D" Methode und der Höchstwahrscheinlichkeitsmethode entnommenen Faktoren wurden in Wechselbeziehung zur *Grundfrequenz* zum Grundfrequenzstörungsquotienten und zum Amplitudenstörungsquotienten gebracht Die Ausserungen von neun *normalen und fünfzehn pathologischen Ver*suchspersonen so wie neun zusammengesetzte Vokalproben wurden untersucht Der erste Faktor war auf die *Bewertung der Stimmeigen*schaft gerichtet und stand auch in Beziehung *zur Amplitudenstörung. Der zweite Faktor*

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SUPPLEMENT 340

The Histopathology of Meniere's Disease

BY

FRANCISCO ANTOLI-CANDELA, Jr., M.D

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Formerly: Research Fellow in Department of Otolaryngology Massachusetts Eye and Ear Infirmary and Harvard Medical School Boston

Presently Chief Section of Research and Education Department of E.N.T. National Center of Surgical Specialties of the Spanish Social Security Ramon y Cajal"

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CONTENTS

Introduction

Meniere's disease, so named by Simon Duplay (1872), has been recognized as a clinical entity for over a century. The original paper by Meniere describing the disease entitled "Memoire sur des Lesions de L'Oreille Interne Donnant Lieu a des Symptomes de Congestion Cerebrale Apoplectiforme" was published in 1861. The paper was translated from the original into English by Atkinson in 1961 and into Spanish by Velasco in 1968.

Although the disease has been a well known entity since 1861 and many methods of treating the condition have been proposed, its etiology and pathophysiology have not been precisely determined. The purpose of this paper is to review the histopathology of Meniere's disease in twenty-five temporal bone specimens of twenty individuals and to correlate the pathological changes with the clinical findings.

I Review of the Literature

LIGHT MICROSCOPY FINDINGS

The first description of the histopathology of Meniere's disease was made by Hallpike & Cairns in 1938 from temporal bone specimens of two patients who had died following surgical procedures for partial section of the VIII cranial nerve. One of these individuals had suffered from symptoms of the disease for three years and the other for five years. The most significant finding was dilatation of the endolymphatic systems, an observation which has subsequently been confirmed in numerous further studies. Hallpike & Cairns also described degenerative changes in the organ of Corti and "absence of the normal area of perisaccular connective tissue" in the area of the endolymphatic sac. One ear also showed degeneration of the stria vascularis. They termed the condition "Hydrops Labyrinthi".

Yamakawa (1938) is credited with the second report on the pathology of Meniere's disease although the cases he presented were poorly documented. In 1940, Hallpike added a third case showing hydrops, but in which the sensory and neural elements and stria vascularis were normal. Subsequently, cases with prolonged clinical histories and without evidence of degenerative changes have been reported (Altmann & Fowler Jr 1943). Most authors agree that atrophy of the sense organ can occur in exceptionally severe cases (Kristensen 1961, Lindsay 1967, Schuknecht 1968a).

In 1958 Lindsay described a temporal bone showing *only cochlear hydrops* and in 1942, he described what he called herniations consisting of ballooning out of weak spots in the superior labyrinth. Altmann & Kornfeld (1965) referred to these as out-pouchings to differentiate them from other types of disruption of the labyrinthine membranes. They described the distortions of the labyrinthine walls as either distentions of the membranes "in which the walls "show the same appearance as the remainder of the structure they are derived from" or "circumscribed thin walled out-pouchings". They suggested that the pathogenesis of the out-pouchings was either

specific change other than that which would be expected to occur as the result of aging

ANIMAL STUDIES

Even before the discovery of endolymphatic hydrops as the principal pathological finding in Meniere s disease research was being per formed on the endolymphatic system In 1921 Portmann produced vestibular disturbances in the fish Leiobatus Postinaca by sealing the endolymphatic duct McNally (1926) failed to reproduce similar disturbances in the rabbit by applying pressure and cautery to the endolymphatic sac Guild (1927) injected dye into the basal turn of the cochlear duct of the guinea pig and recovered it in the endolymphatic sac providing the first evidence that the sac might play a role in the physiology of the endolymphatic system

Lindsay (1947) obliterated the endolymphatic sac and duct of the monkey (Macacus Rhesus) but failed to produce changes in the volume of endolymph thus concluding that in the monkey the maintenance of a normal quantity of endolymph does not depend on the endolymphatic sac.

Altmann & Waltner (1947) while using rabbits found that the injection of iron salt solution into the cerebrospinal fluid reached the perilymphatic spaces through the cochlear aqueduct and then passed through Reissner s membrane into the cochlear duct to be absorbed by the stria vascularis These same authors (1950) repeated the experiment in rabbits and monkeys and concluded that the endolymph is resorbed in the stria vascularis and only "substances which are difficult for resorption by the regular cochlear mechanism are carried to the sac where they are broken up by the phagocytes and eventually resorbed"

Lindsay et al (195?) Schuknecht & Kimura (1953) van Egmond & Brinkman (1956) Schuknecht & Seifi (1963) and others per formed ablation studies on the endolymphatic sac but none were clearly able to produce endolymphatic hydrops.

Naito in 1959 and Kimura & Schuknecht in 1965 succeeded in producing endolym phatic hydrops by obliteration of the endolymphatic sacs while working with guinea pigs In 1968 Schuknecht achieved the same results in cats These studies showed for the first time that the endolymphatic sac plays an important role in fluid physiology of the inner ear

In guinea pigs the endolymphatic hydrops occurred within two weeks of blocking the endolymphatic duct while in cats definite hydrops could only be found after survival times of two to three years Thus it became clear that previous failures to produce hydrops in cats were due to the short post ablation survival times These and subsequent studies have also shown that loss of the endolymphat ic sac function not only produces hydrops but also degenerative changes in the organ of Corti and cochlear neurons more severe in the apices of the cochleae (Schuknecht & Kimura 1953)

II Histopathologic Findings in the Labyrinthine Membranes

MATERIAL AND METHOD

This report is based on the study of twenty five temporal bones from twenty individuals with Meniere s disease The disease was unilateral in fifteen and bilateral in five All patients had histories consistent with Meniere s disease The temporal bones were removed with the bone plug cutter from two to twenty-four hours after death, placed in formaldehyde and heidenhain susa solution

rupture of the inner wall of the labyrinth with ballooning out of the outer layer or atrophy of both layers in restricted regions with herniations into the perilymphatic space

Lawrence & McCabe (1959) reported healed ruptures in Reissner s membrane and Schuknecht (1962) described healed disruptions in the utricle and semicircular canals

Lindsay (1960) believed that rolled up margins in areas of complete discontinuity or rupture of the membranes indicated ante mortem changes and not artifact Altmann & Kornfeld (1965) because they found it difficult to believe that two ruptures could occur in the same structure doubted the validity of this interpretation

Two temporal bones have been described with fistulae between the utricle and saccule (Altmann & Fowler 1943 Kristensen 1961) Both were found in individuals with long standing disease and severe symptomatology Hallpike & Cairns (1938) and Altmann & Fowler (1943) described blebs on the membranous labyrinths of ears exhibiting the hydrops of Meniere s disease Lempert (1952) found them in surgical specimens removed during labyrinthectomy and termed them vesicular epithelial excrescences He believed them to be a sign of chronic progressive degenerative changes and suggested that they might be responsible for the endolymphatic hydrops These excrescences are also known to occur in normal specimens and therefore cannot be associated specifically with Meniere s disease

Degenerative changes in the epithelium of the endolymphatic sac have been described by Hallpike & Cairns (1938) and Hallpike & Wright (1940) and more recently by Gussen (1971) and Arenberg et al (1971) However these changes do not seem to be consistently present in ordinary light microscopic preparations (Yuen & Schuknecht 1972)

In 1968*a* Schuknecht described a formation resembling choroid plexus in the region of the ductus reuniens in several ears of individuals with Meniere s disease He thought that although these formations were not consistently found they might have a secretory function and thus be of pathogenic significance in the development of endolymphatic hydrops. In a more recent report Gussen (1971) found a similar formation in the intermediate portion of the endolymphatic sac in one ear with endolymphatic hydrops She then reviewed 170 normal specimens and found only one such structure In the same report she described anomalies of the membranous crus commune and the bony endolymphatic duct She concluded that Meniere s disease can either be idiopathic or secondary to these anomalies

ELECTRON MICROSCOPY FINDINGS

The use of electron microscopy in the study of Meniere s disease is complicated by the inaccessability of the membranous labyrinth However removal of tissue during surgical procedures (e g labyrinthectomy) has provided some specimens for study

Peitrantoni & Iurato (1960) in a study of one crista ampullaris found vacuolization cytoplasmic inclusions of unknown nature and absence of cilia in the sensory cells They also noticed vacuolization and vesicles in the supporting cells Litton & Lawrence (1961) Friedmann et al (1963) and Ireland & Farkashidy (1963) showed similar findings in surgical specimens In a more recent report Hilding & House (1964) studied specimens of membranous labyrinth removed from ears with acoustic neuromas and found similar changes suggesting that the alterations might be due to surgical trauma. They concluded the vacuolizations were more frequent in Meniere s ears but stated that it is not possible to say at this time whether this change is a fixation artifact change of age reaction to toxin or some combination of these factors

Kimura & Schuknecht (1970*a* 1970*b*) examined the stria vascularis in surgical specimens and also failed to recognize any

Fig. 1 (Case) Distended ductus reuniens occupying much of the vestibule. There is an endolymph-to-endolymph fistula between the saccule and the distended ductus reuniens.

Fig. 2 (Case E. W., not included in the volumetric study) Distended saccule with fibrous tissue proliferation under the footplate of the stapes and lateral wall of the vestibule.

decalcified in trichloroacetic acid solution and embedded in celloidin All specimens were sectioned at a thickness of 20 μm and every tenth section stained with hematoxylin and eosin and mounted on glass slides (Schuknecht 1968*b*)

Special care was taken to cut the horizontal sections in the plane of the modiolus of the cochlea in order to facilitate graphic reconstruction of the sensory and neural elements of the cochlea and stria vascularis (Guild 1921 Schuknecht 1953) Of the twenty five ears with Meniere s disease eighteen were in an excellent state of histological preservation and preparation and therefore suitable for detailed histological study and graphic reconstruction Only part of one other specimen (Fig. 45) was suitable for study In the fifteen individuals with unilateral Meniere s disease the opposite ear was available and suitable for study and detailed graphic reconstruction in six

1 The inferior labyrinth (Cochlea and saccule)

Membrane dilation

Dilation of the cochlear duct is present in all nineteen specimens Several show collapse presumably following previous dilation Although herniation of Reissner s membrane through the helicotrema has been frequently described in the literature (Hallpile 1938 Rollin 1940 Lindsay 1942 1944 1960 and 1967 Kristensen 1961 Altmann 1965 Kohut 1972 Blättler et al 1973) this finding is present in only two of the nineteen specimens (Figs 33 and 43) Four others (Figs 35 36 40 and 41) however show nearly complete filling of the scala vestibuli in the apical region by the distended cochlear duct and five cochleae (Figs 33 35 37 42 and 43) show almost complete filling of the scala vestibuli by the cochlear duct at points other than the cecum vestibulare

Herniation into the vestibule of the cecum vestibulare of the cochlear duct or ductus reuniens as previously described by Schuknecht (1962) and Altmann (1965) is present in eight ears (Figs 30 31 35 38 39 4? 44 and 45) One of these shows a fibrous adhesion between the herniated membrane and the footplate and lateral wall of the utricle (Figs 1 and 31)

The saccule is dilated in all the specimens. One ear shows only mild dilation of the saccule and cochlear duct (Fig 29) In nine ears the saccular wall is in contact with the stapes footplate (Figs 32 33 34 35 36 38 40 41 and 43) with three showing fibrous adhesions to the footplate (Figs 33 34 41) (See Fig 2) In specimen sixteen the distended saccular wall also lies in contact with a distended cochlear duct In two ears (Figs 38 and 45) the enlarged saccule extends into the nonampulated end of the lateral semicircular canal a condition previously described by Altmann (1943) Lindsay (1944) Day (1949) Altmann (1965) and Lindsay (1967) (Fig 3)

In most specimens the reinforced area of the saccular wall retains its normal position suggesting that it is more resistant to distortion by the effects of the endolymphatic hydrops (Fig. 4)

Membrane collapse

It is not always possible to determine whether collapse of labyrinthine membranes represents postmortem or antemortem changes as pointed out by Schuknecht (1968*c*)

Membranes which are distended and thus possibly weakened may be more susceptible to preparation artifacts A good example of antemortem collapse is seen in ear four which has a collapsed but previously distended cochlear duct In the collapsed lumen there is acidophilic fluid and precipitate (Figs 5 and 6) Ears two and four (Figs 28 and 30) show partially collapsed saccular walls and ear nine (Fig. 35) shows a previously distended cochlear duct which appears to have been compressed and collapsed against the foot

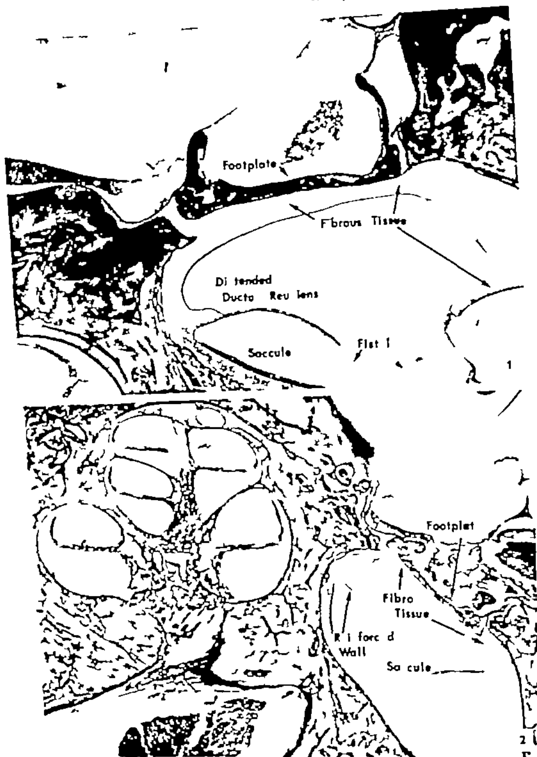


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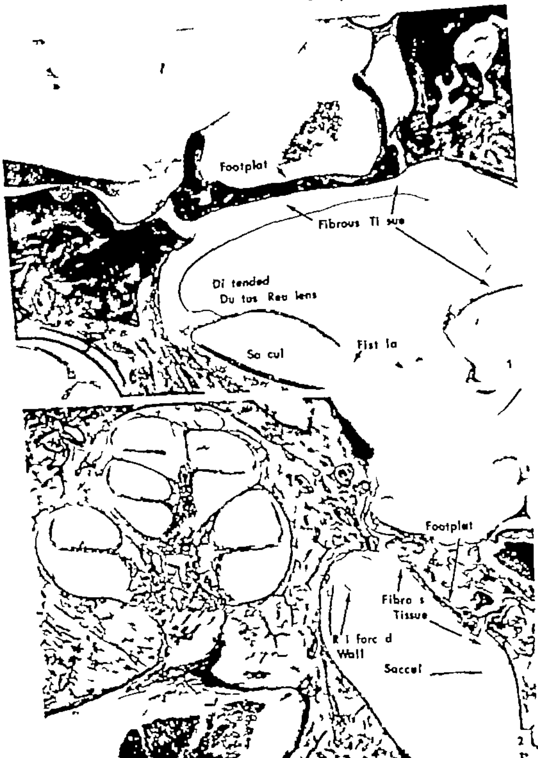


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plate and lateral wall of the vestibule by the distended saccule (Fig 7)

Membrane ruptures

The interpretation of the breaks in the con tinuity of membranes must be based on associated morphological changes as well as on the quality of the histological preparation For example a rupture in the membranous labyrinth adjacent to a small fissure in the bony labyrinth would be suggestive of preparation artifcat Also breaks in the mem branes of an opposite ear (without Meniere s disease) would suggest artifact The diffi culties in making these judgements have been discussed by Lindsay (1960) Schuknecht (1962) and Altmann (1965) However taking these factors into account it appears that there are antemortem ruptures of Reissner s membrane in eight ears (Figs 31 33 34 36 37 39 40 and 45) and in the saccule in eleven ears (Figs 31 32 34 35 37 38 39 40 43 44 and 45) Ear five (Fig 31) shows three ruptures in the cochlear duct and one in the saccule Ear eleven (Fig. 37) shows one in Reissner s membrane and two in the saccule and ears eight thirteen fourteen and nineteen (Figs 34 39 40 and 45) show one rupture in Reissner s membrane and one in the saccule

Kristensen (1961) and Blättler et al (1973) described ears in which Reissner s membrane was herniated through the helicotrema and extended into the second turn without ruptures These extensive dilatations without ruptures suggest that should there be an in crease in endolymphatic pressure it is a slow and insidious process

In six of eight ears with rupture of Reissner's membrane the ruptures occurred in the area of maximum dilatation (Figs 33 34 37 39 40 and 45) and in only two did it occur elswhere (Figs 31 and 36) (see Fig. 8)

Study of the saccules show that ruptures are present in each of two ears with severe disten tion (Figs 38 and 45) eight of ten with moderate distention (Figs 32 34 35 37 39 40 43 and 44) and one of five with mild distention (Fig 31) Altmann & Kornfeld (1965) are of the opinion that it would be improbable that more than one rupture would occur in the same structure This obviously would pertain if healing of the breaks did not occur This point will be further discussed in the section describing ruptures in the superior labyrinth

Ear five (Fig. 29) which shows a large rupture of Reissner's membrane in the basal turn also shows atrophy and encapsulation of the tectorial membrane in the same region (Figs 8 and 31) This was the only ear in which there was a spatial correlation of a break in Reissner s membrane with another structure of the cochlear duct

Because all ears presented relatively uniform patterns of threshold loss on audiometric testing it is obvious that the ruptures of Reissner s membrane did not create a selective loss of hearing in the auditory spectrum

2. The superior labyrinth (*Utricle and semicircular canals*)

Membrane dilatation

The walls of the superior labyrinth are thicker and probably more resistant to distortion In none of these specimens was the utricular dilatation as striking as that described by Lind say (1942)

Membrane collapse

Severe collapse is rarely found in the superior labyrinth and in only two ears eleven and six (Figs 37 and 32) is there collapse in this region In ear eleven (Fig 37) the collapse is thought to be antemortem because (1) the utriculo-endolymphatic valve is compressed by an enlarged saccule (Fig 9) whereas in all other specimens the utriculo-endolymphatic valve is normal or open (Fig 10) (2) there is an eosinophilic pink staining fluid filling the superior labyrinth (Fig. 9) probably an indica

F (Case 9) Severe dilatation of the saccule. The herniated ochlear duct is compressed against the lateral all of the vestibule by the distended saccule. Note the utriculo-endolymphatic valve is open.

Fig. 8 (Case 5) Rupture of Reissner membrane and *encapsulation of the tectorial membrane.*

Fig 9 (Case 11) Severe dilatation of the saccule *compressing the utriculo-endolymphatic valve* There is an acidophilic staining fluid in the utricle and semicircular canals.

Fig 10 (Case 6) The utriculo-endolymphatic valve is open.

11

12

F 11 Case 11 Collapsed utricular [illegible] all showing [illegible] formations and areas of disruption of the sen- [illegible] epithelium of the utricular macula

Fig 12 (Case 6) Collapsed wall of the ampulla of the superior semicircular canal Cystic degeneration of the subepithelial tissue of the crista

Fig 9 (Case 11) Severe dilatation of the saccule compressing the utriculo-endolymphatic valve There is an acidophilic staining fluid in the utricle and semicircular canals.

Fig 10 (Case 6) The utriculo-endolymphatic valve is open.

Fig 13 (Case R. B not included in the volumetric study) Cystic degeneration of the posterior canal There is acidophilic staining fluid filling the cysts. There is an area of degeneration of the ampullary wall.

Fig 14 (Case 7) Rupture of the ampulla of the posterior semicircular canal. This is the most common site for ampullary ruptures. The fistula appears to lead to pouch ith intact walls.

tion of interference with fluid resorption and (3) the utricular macula shows epithelial adhesions to the collapsed utricular wall *cystic formations and disruption of the epi* thelium (Fig 11) In case six (Fig. 12) there is not only displacement of the ampullary wall of the superior canal but also cystic degeneration of the subepithelial tissue with an acidophilic staining fluid filling the cyst These changes could be secondary to the membranous collapse although similar changes have been found in the posterior canal ampulla of another specimen which did not show a collapse of the ampullary wall (Fig. 13) Degeneration of the sensory epithelium of the vestibular system is rare in Meniere s *disease for this is the first report of this* pathological change

Membrane ruptures

Nine of the utricules show discontinuity of the membranous walls (Figs 29 31 33 35 36 38 40 43 and 45) five in the superior half and seven in the inferior half of the utricle

There are fifteen ruptures in the ampullae three in the lateral canal (Figs 33 40 and 45) three in the superior canal (Figs 40 43 and 45) and nine in the *posterior canal (Figs 33* 37 40 43 45) In two ears the ampullae show two outpouchings (Figs 37 and 45) and in one ear there are three (Fig 43) Outpouchings in the semicircular canal ampullae are most often *found* surrounding the cristae and area semilunata as shown in Fig 14

The *defects in the walls of the superior* halves of the utricles and the semicircular canal ampullae correspond to those described by Schuknecht (1968*a* 1968*c*) (Figs 15 and 16) The ruptures in the inferior part of the utricle appear similar to those seen in Reissner s membrane and the saccule with actual openings into the endolymphatic space. Five of these latter ruptures were found very close to the utriculo-endolymphatic valve area (Figs 35 36 38 40 and 45)

Only one rupture was found in the semicir cular canals (Fig 43) and this is located in the non ampullated end of the posterior semi circular canal near the common crus The outpouching type of rupture is found characteristically in the ampullae and superior halves of the utricles Schuknecht s interpretation of the outpouchings as representing healed ruptures seems to be supported by recent experimental observations of Kimura & Schuknecht (1975) who have demonstrated *the remarkable propensity of the membranous* labyrinth to heal

III Volumetric Study

MATERIAL AND METHOD

Material

Histological preservation and preparation are *suitable to permit volumetric studies* of the cochlear ducts of seventeen specimens and the ampullae of the posterior and superior semicircular canals in six cases in which the opposite normal sides are available

The ampullae of the lateral canals and the utricles could not be studied because of the plane of sectioning.

Twenty temporal bones from ten individuals without clinical or histopathological evidence of pathology are studied and serve as a *control*

Method

The word volume" has been chosen to express an estimate of the volume derived from the cross sectional areas of the cochlear spaces at different levels along its length

To estimate the *increase in area of the* cochlear duct (*B* in Fig. 20) and corresponding decrease in area of the scala vestibuli (*C–B* in Fig. 20) six points have been selected

Fig. 13 (Case R. B. not included in the volumetric study). Cystic degeneration of the posterior canal. There is acidophilic staining fluid filling the cysts. There is an area of degeneration of the ampullary wall.

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The defects in the walls of the superior halves of the utricles and the semicircular canal ampullae correspond to those described by Schuknecht (1968*a* 1968*c*) (Figs 15 and 16) The ruptures in the inferior part of the utricle appear similar to those seen in Reissner s membrane and the saccule with actual openings into the endolymphatic space. Five of these latter ruptures were found very close to the utriculo-endolymphatic valve area (Figs 35 36 38 40 and 45)

Only one rupture was found in the semicircular canals (Fig. 43) and this is located in the non ampullated end of the posterior semi circular canal near the common crus The outpouching type of rupture is found characteristically in the ampullae and superior halves of the utricles Schuknecht s interpretation of the outpouchings as representing healed ruptures seems to be supported by recent experimental observations of Kimura & Schuknecht (1975) who have demonstrated the remarkable propensity of the membranous labyrinth to heal

III Volumetric Study

MATERIAL AND METHOD

Material

Histological preservation and preparation are suitable to permit volumetric studies of the cochlear ducts of seventeen specimens and the ampullae of the posterior and superior semicircular canals in six cases in which the opposite normal sides are available

The ampullae of the lateral canals and the utricles could not be studied because of the plane of sectioning.

Twenty temporal bones from ten individuals without clinical or histopathological evidence of pathology are studied and serve as a control

Method

The word "volume has been chosen to express an estimate of the volume derived from the cross sectional areas of the cochlear spaces at different levels along its length

To estimate the increase in area of the cochlear duct (*B* in Fig 20) and corresponding decrease in area of the scala vestibuli (*C–B* in Fig 20) six points have been selected

Fig. 13. (Case R. B., not included in the volumetric study): Cystic degeneration of the posterior canal. There is acidophilic staining fluid filling the cysts. There is an area of degeneration of the ampullary wall.

Fig. 14. (Case 7): Rupture of the ampulla of the posterior semicircular canal. This is the most common site for ampullary ruptures. The fistula appears to lead to a pouch with intact walls.

tion of interference with fluid resorption and (3) the utricular macula shows epithelial adhesions to the collapsed utricular wall cystic formations and disruption of the epithelium (Fig 11) In case six (Fig 12) there is not only displacement of the ampullary wall of the superior canal but also cystic degeneration of the subepithelial tissue with an acidophilic staining fluid filling the cyst These changes could be secondary to the membranous collapse although similar changes have been found in the posterior canal ampulla of another specimen which did not show a collapse of the ampullary wall (Fig. 13) Degeneration of the sensory epithelium of the vestibular system is rare in Meniere s disease for this is the first report of this pathological change

Membrane ruptures

Nine of the utricules show discontinuity of the membranous walls (Figs 29 31 33 35 36 38 40 43 and 45) five in the superior half and seven in the inferior half of the utricle

There are fifteen ruptures in the ampullae three in the lateral canal (Figs 33 40 and 45) three in the superior canal (Figs 40 43 and 45) and nine in the posterior canal (Figs 33 37 40 43 45) In two ears the ampullae show two outpouchings (Figs 37 and 45) and in one ear there are three (Fig 43) Outpouchings in the semicircular canal ampullae are most often found surrounding the cristae and area semilunata as shown in Fig. 14

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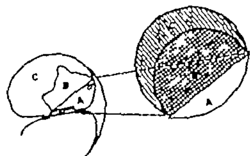
To estimate the increase in area of the cochlear duct (*B* in Fig. 20) and corresponding decrease in area of the scala vestibuli (*C–B* in Fig. 20) six points have been selected

Fig. 17 (Case 5. 5 not included in the volumetric study). Distended utricle showing two ruptures with herniations.

Fig. 18 (Case 17). Ampulla of the posterior canal showing an atrophic area of its membranous wall.

Fig 15 (Case 7) Ruptured utricle The fistula appears to lead to a pouch with a very thin but i tact wall

F g 16 (Case 14). Thin wall herniation of the ampulla of the posterior canal showing f brous adhesions to the endosteal wall.



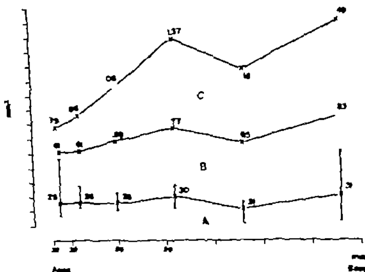


Fig. 20. The upper diagram is a schematic representation of a section perpendicular to the organ of Corti. (*A*) normal cochlear duct, (*B*) increase in area of the cochlear duct, (*C*) scala vestibuli. The lower shows the average area in cases one through seventeen. (*A*) cochlear duct, (*B*) distended cochlear duct, (*C*) scala vestibuli. The site of the measurements (*H* *LT* *UT* LT_m UT_m and T_3) correspond to the 2, 12, 19 25 29 and 31 mm regions in the cochlea.

Table I

Bilateral cases ar 1 and 2 3 and 11 6 and 9 7 and 8, 5 and 14 A ascending (20 or more db slope) F=flat, D=descending (20 or more db slope)

Case	Age at death	Tone Lapse audio. to death	Duration of disease (years)	Average hearing loss (500 to 8 000 Hz)	Incr. in area cochlear duct
1	44	4 y	6	28 (A)	77.20%
2	44	4 y	6	29 (A)	37.44%
3	62	2 y	2	41 (F)	101.60%
4	66	5 m	3	65 (F)	98.49%
5	1	1 y	6	63 (F)	120.61%
6	62	5 d	18	63 (F)	32.43%
7	65	4 y	34	79 (F)	304.47%
8	65	24 y	34	85 (F)	260.05%
9	62	5 d	18	91 (F)	424.83%
10	56	1 m	10	35 (F)	102.37%
11	53	2 y	2	72 (D)	274.24%
12	74	3 y	12	81 (D)	144.69%
13	65	9 y	15	81 (D)*	122.34%
14	71	1 y	6	No audio	141.80%
15	73		10	No audio.	77.80%
16	53		16	No audio.	225.80%
17	87		7	No audio.	364.42%
18	80		27	No audio.	
19	70	3 w	—	40 (F)	

* Presbycusis.

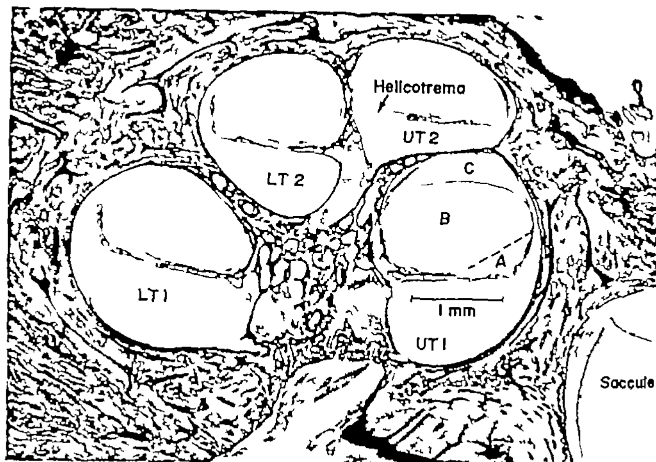


Fig 19 (Case 9) Midmodiolar section. The dotted line represents Reissner's membrane assuming its normal position. This case and number six are the right and left sides of the same patient. Both sides present a small (30 mm.) cochlea Lower turn one (LT_1) upper turn one (UT_1) Lower turn two (LT_2) upper turn two (UT_2). Assumed normal cochlear duct (A) increased volume (B) and scala vestibuli (C)

along the length of the cochlea A midmodiolar section has been chosen since it is perpendicular to the cochlear partition at five different levels corresponding to the 12 19 25 29 and 31 mm cochlear regions The sixth level has been arbitrarily selected in the 2 to 3 mm region

For each section a drawing is made by projecting the slides with a Bausch and Lomb slide projector (47×) The points at which Reissner s membrane is attached to the limbus spiralis and basilar crest (spiral ligament) are determined by histological appearance or arbitrary decision These points are shown as (a) and (a) in Fig. 20 From (a) to (a') the following lengths were measured (1) the length of the distended Reissner s membrane (2) the length of the walls limiting the scala vestibuli (3) the length of the walls limiting the scala media

In order to measure the length the outlines of each of the described spaces are traced with a graphical input device (SAC graph/pen) attached to a PDP 8/E computer The computer determined the required lengths by sampling the contours at an interval which would correspond to 18 micrometer on the slide A special computation procedure is used to estimate the areas The fully distended membrane was assumed to have formed an arc convex into the scala vestibuli and the normal position of Reissner s membrane is taken to be a straight line between (a) and (a') in Fig. 20 The computer program then computed an equivalent area for each of the lengths (1) (2) and (3) above by assuming that each

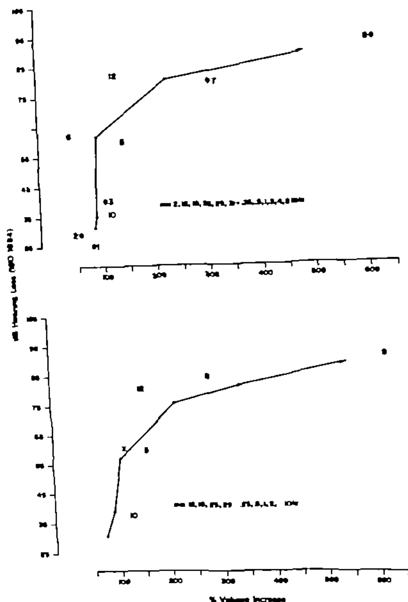
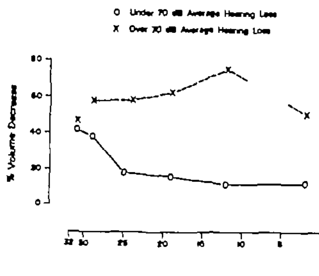


Fig 22 Volumetric study Average percentage volume increase versus average hearing loss for cases one through twelve. The number on the data points indicat the case number (*Top*) All measurements and cor responding frequencies are included (*Bottom*) Measurements on mm 2 and 31 and their corresponding audiometric values have been excluded.

13 Fig. 3) or there is no response to all the tested frequencies (case 14 Fig. 40)

In the twelve ears that were studied, the data permitted a correlation between the hearing loss and the magnitude of increase in endolymph of the cochlear duct. The average increase is computed for two groups. one with hearing loss (ISO 1964) greater than seventy decibels (cases 7 8 9 11 12, *Table I*) and the other with *hearing loss less than* seventy decibels (cases 1 2, 3 4 5 6, 10) The data shows a greater increase in endolymph in the group of ears with the greater hearing loss (Fig. 1). The curve for the cases with a hearing loss less than 70 db has a higher percentage of volume increase in the apical turn (mm 25 to 31) of the cochlear duct than in the middle and basal turns. The curve in the advance cases has a greater percentage of volume increase in the middle and basal



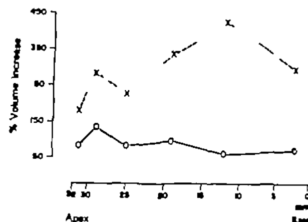


Fig 21 (*Right*) Average ratio of increase in volume of endolymph to the normal volume (*B/A* Fig. 20) — group of individuals with a hearing loss less than 70 db group of individuals with a hearing loss greater than 70 db (*Left*) Average ratio of increase of endolymph to remaining perilymph in the scala vestibuli (*B/C* Fig. 20) — group of individuals with hearing loss less than 70 db group of individuals with hearing loss greater than 70 db (see text, Volumetric Study")

boundary formed an arc passing through (*a*) and (*a'*)

The percentage increase in area is obtained by dividing the distended' measurement (*B*) by the normal measurement (*A*) thus % increase = *B*/*A* (Fig 20) The ratio of the areas of increased endolymph to remaining perilymph is also determined (*B*/*C* Fig 20) These measurements made at six points (2 12 19 25 29 and 31 mm) are adjusted to fit a uniform 32 mm cochlear model in the cochleae which measure longer or shorter than 32 mm (see Fig 19)

The areas of the superior and posterior semicircular canal ampullae are measured in sections cut at right angles to the middle region of the cristae in this case the cord (*a–a*) corresponds to the edges of the cristae

Studies have been done on the cross section of the cochlear duct scala vestibuli and scala tympani in the normal human (Weber 1949) and guinea pig (Fernandez, 1952) Kimura, in 1967 also studied the percentage of volume increase in guinea pigs with induced hydrops

Because this method is based on the assumption that the limiting walls of the inner ear spaces form an arc the areas thus obtained are larger than the actual ones Therefore the available data from previous studies cannot be compared to the present study in absolute values For this reason we shall refer to relative values

I The Inferior labyrinth

With the previously described method the cross sectional areas are determined for the cochlear duct scala vestibuli and distended cochlear duct Obviously the area of the scala vestibuli decreased as the area of the cochlear duct increased Although the precise physiological functions of the perilymph are unknown it is possible that a decrease in perilymph volume as well as an increase in endolymph may be of pathological significance

A possible relationship of the two fluids has been suggested by previous authors (Altmann & Waltner 1950 Tonndorf 1962 Ilberg & Vosteen 1969)

Cases excluded from this study are those in which the audiometries are not available or the volumetric study could not be performed Cases thirteen and fourteen have also been excluded because there is audiological evidence of presbycusis in the opposite side (case

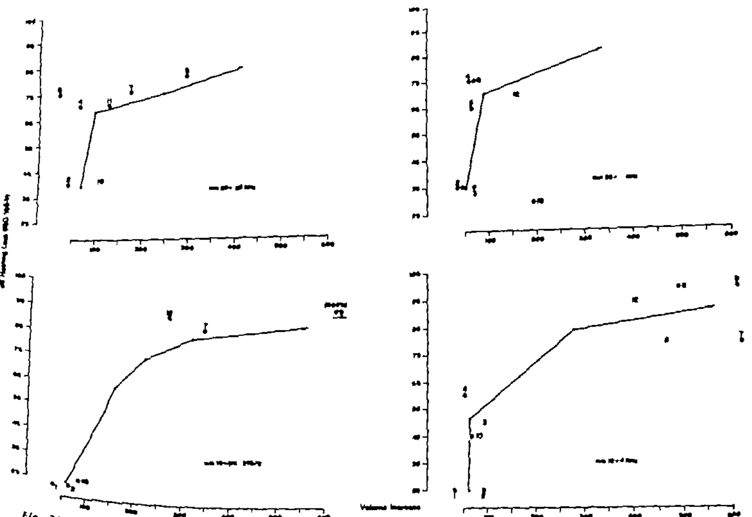


Fig. 24 Volumetric study. Volume increase versus hearing loss, direct correlation. Cases one through twelve—cochlear measurements and hearing evaluation for mm 29 and 0.25 KHz, mm 25 and 0.5 KHz, mm 19 and average hearing loss for 1 and 2 KHz, and mm 12 and 4 KHz.

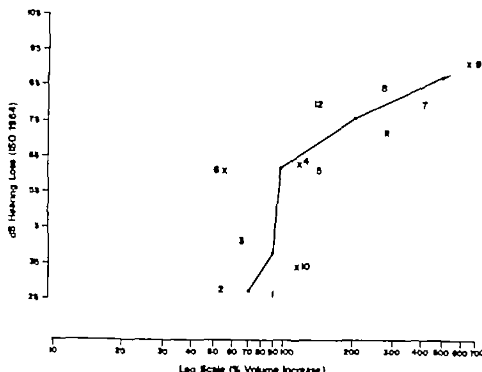


Fig 23 Volumetric study Average percentage volume increase versus average hearing loss for cases one through twelve Measurements on mm 2 and 31 have been excluded Note logarithmic horizontal scale.

turns of the cochlear partition (mm 2 to 20 Fig 21)

A clear correlation to the audiometric pattern could not be found by grouping the cases according to their flat ascending or descending patterns (Table I 20 db criterion)

In order to evaluate the relationship of volume increase versus hearing loss for each case the mean thresholds for the frequencies 0 25 0 5 1 2 4 and 8 KHz, were plotted against the corresponding cochlear measurements (Fig. 22) The data demonstrates a direct relationship between them. Because the range of measured areas for the normal cochelar duct in the extreme regions are very broad (0 48 mm² and 0 40 mm² respectively Fig. 20) the same correlation has been made excluding the measurements for the hook region (mm 2–3) and the third turn (mm 31) Their corresponding audiometric values were also excluded Under these circumstances the curve becomes smoother (Fig 22) Since the increase in intensity in the clinical evaluation of the hearing loss is exponential (db) the values of the volume increase have been plotted on a logarithmic scale in fig 23 The curve thus obtained has two sections the first having a very steep slope up to 70 db (over 100 db/Dec) second with a slower rise (40 db/Dec) for hearing losses over 70 db This correlation has also been found for each location of measurement (UT2 LT2, UT1 LT1) and their corresponding representation in the audiogram (Fig 24)

The wide range in the measurements could be explained by the inevitable differences in the plane of sectioning which are more pronounced at each end of the cochlea (Fig.

Table II *Volumetric study posterior and superior ampullae*

	Average (mm³)	Range
Normal (N 10)		
Superior amp. R.	1 857	2.825–1.387
Superior amp. L.	1 720	2 108–1 270
Posterior amp. R.	1 813	2.142–1 304
Posterior amp. L.	1 933	2.343–1 604
All ampullae	1 830	
Difference Rt./Lt. (Sup. + Post.) = 0 0087 mm³		
Meniere s unilateral (N-6)		
Superior amp M's	1 682	2.157–0.887* (1 531)
Superior amp. Op s	1.826	2.693–0 934 (1 435)
Posterior amp. M's	2.033	2.734–1 624
Posterior amp. Op s	1 904	2.546–1.584
Difference M's/Op s (Sup + Post.) = 0.0075 mm³		

* Small ampulla. Next value between brackets.

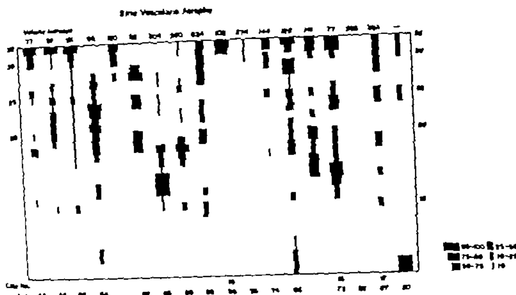


Fig. 26 Evaluation of the stria vascularis. The black columns represent the percentage of strial atrophy The figures on the left of the graph indicate the site along the cochlea in millimeters.

The average area for the superior canal ampullae is 1 826 mm² (range 2.693–0 934) in the normal side and 1 682 mm² (range 2.157–0.887) in the Meniere s side The average area for the posterior canal ampullae is 1 904 mm² (range 2 546–1 584) in the normal side and 2.033 mm² (range 2.734–1.624) in the Meniere s side The difference between Meniere s side and the opposite normal side is 0 144 mm² (larger in Meniere s side) for the superior canal and 0 129 mm² (larger in the normal side) for the posterior canal

Differences in the areas of section between the normal and pathological ears in unilateral cases of Meniere s disease are not significant (Table II)

IV Cochlear Sensory and Neural Structures

1 THE ORGAN OF CORTI

In all the ears, the hair cell population appeared to be normal for age Losses at the basal ends of the cochleae are presumed to be caused by aging and are found in ears without Meniere s disease In four cases with unilateral Meniere s disease the hair cell populations appeared to be identical to that of the opposite ears In case four (fig. 30) the opposite ear shows a severe *hair cell loss* of unknown cause in the first 5 mm of the cochlea. In case ten (Fig. 36) the opposite ear shows a hair cell loss in the 7 to 13 mm region and a hearing loss for 4 KHz and 8 KHz which is compatible with *unilateral* acoustic trauma. These observations relate *only* to the presence or absence of sensory cells, which does not necessarily imply that the present cells are *functional*

2. THE SPIRAL GANGLION

1 *Ganglion cell loss due to aging*

In the interpretation of the findings in the spiral ganglion cell population the age of the patient *has to be taken* into *consideration* for it has been *established* that there is a ganglion cell *loss of varying degree in* the basal turn of

Ganglion Cell Population

Fig 25 Evaluation of the spiral ganglion The black columns represent the percentage of ganglion cell loss The figures one through thirty-two on the left of the graph indicate the site along the cochlea in millimeters.

20) The presence of the helicotrema in the mm 31 complicates the determination of the boundaries of the scala vestibuli

Since the angle of section is the same for all the measurements made at the same location small changes in this angle should not have a significant effect on the percentage values

2. The superior labyrinth

Measurements of corresponding ampullae of right and left ears were made on twenty temporal bones from ten individuals with no clinical or pathological evidence of otological disease (Table II) According to the previously described method the average area for the superior and posterior canal ampullae is 1 830 mm² (range 2 825–1 270) The average area for the superior ampullae is 1 788 mm² (range 2 825–1 270) and for the posterior ampullae 1 873 mm² (range 2 343–1 304) The difference between the average superior and posterior ampullae is 0 085 mm² The difference between right and left is 0 137 mm² for the superior ampullae and 0 ?09 mm² for the posterior ampullae

In the six individuals with unilateral Meniere s disease in which the opposite normal side was available for study the average area of the superior and posterior ampullae in the normal side is 1 865 mm² (range 2.693–0 934) and the average area in Meniere s is 1 857 mm² (range ? 734–0 887)

Table III *Loss of cochlear neurons*

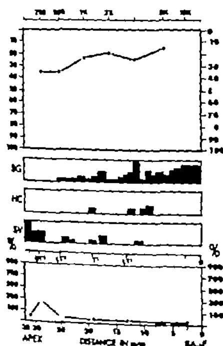
Location	Estimated % ganglion cell loss		
	Age		
	Under 65	65 and over	Difference
0 to 10 mm	51%	66%	15%
11 to 25 mm	37%	43%	6%
26 to 32 mm	16%	18%	2%

Table IV *Loss of cochlear neurons*

Location in the cochlea	Estimated % ganglion cell loss		
	Vol. incr		
	Under 130%	Over 130%	Difference
0 to 10 mm	62%	61%	1%
11 to 25 mm	41%	39%	[illegible]
26 to 3[illegible] mm	13%	[illegible]3%	10%

Fig 27

CASE No 1



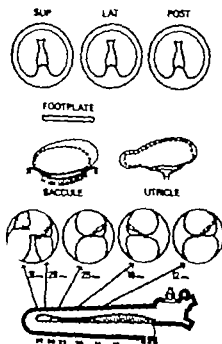
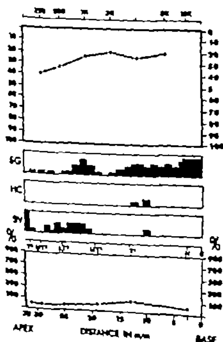
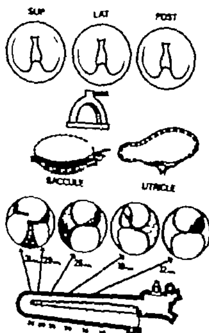


Fig 28

CASE No 2





the cochlea due to aging (Otte 1968) To evaluate the role of aging as a cause for loss of ganglion cell population in these specimens two groups were compared those in the age group 0–64 years and those over 64 years (Table III Fig. 25)

The average age in the first group is 54 years (Cases 1 2 3 6 9 10 11 16 Table I) The average age for the group of individuals over 65 years is 70 years (Cases 4 5 7 8 12 13 14 15 17 Table I) The average volume increase is 189% for the "younger' age group and 181% for the "older" age group

The difference in the ganglion cell population of these groups is minimal in the 25 to 32 mm cochlear region (Table III) In the 10 to 25 mm region there is a small difference and it becomes significantly larger for the "older group in the first 10 mm of the cochlea. This finding is consistent with previous studies (Otte 1968)

2 Ganglion cell loss due to hydrops

A correlative study has also been made grouping these cases according to the percentage of volume increase The first group (N 9) including cases with a percentage of volume increase less than 130% (average 90%) and the second (N-8) including cases with a percentage of volume increase over 130% (average 292%) The average age for the first group is 66 years and the average age for the second group is 60 years A correlation of ganglion cell loss to the volume increase was found only for the last 7 mm of the cochlea (Table IV)

3 THE STRIA VASCULARIS

There is atrophy of the stria vascularis in all but one of the specimens (case 16 Fig. 42) (see Fig. 26)

The strial atrophy is more severe in the apical two-thirds of the cochleae in all cases. There is a striking similarity between the pattern of the atrophy in these specimens and that found in presbycusis (Schuknecht & Ishii 1966 Belal 1974 Schuknecht et al 1974) (see Fig. 26)

V Synopsis

The following is a display of the nineteen (Figs 27 to 45) cases studied Each figure represents a single case Some clinical data for these cases are available in Table I The pathological findings and volumetric study have been represented in two diagrams as follows

1 Left diagram

The upper graph shows pure tone thresholds with the stimated frequency distribution on the anatomical frequency scale that is in accordance with their spatial location along the cochlear duct (Schuknecht 1968*b*)

The second graph (S G) presents the spiral ganglion evaluation given in percentages of ganglion cell loss (black)

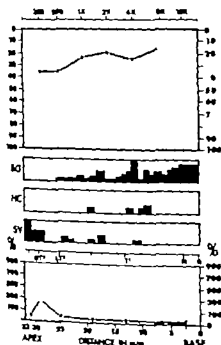
The third graph (H C) presents the hair cell population given in percentages of hair cell loss (black)

The fourth graph (S V) presents the evaluation of the stria vascularis given in percentage of degeneration (black)

The lower graph presents the percentage of volume increase in endolymph (B/A Figs 19 20) determined in six regions of the cochlea corresponding to H=hook region (2 to 3 mm region) LT_1=lower half of the first turn (12 mm region) UT_1=upper half of the first turn

Fig 27

CASE No 1



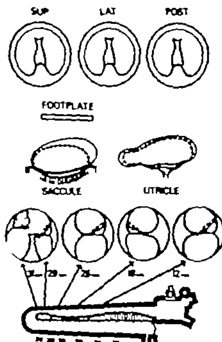
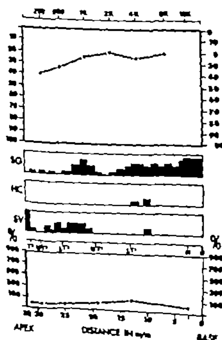


Fig 28

CASE No 2



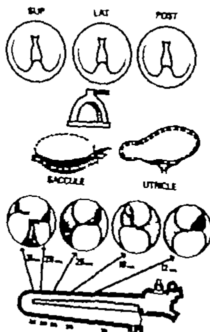
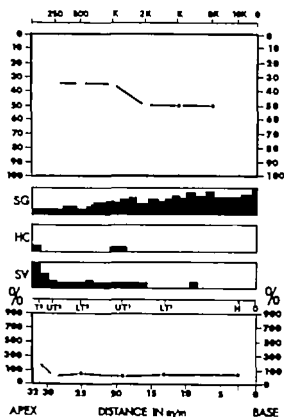


Fig 29

CASE No 3



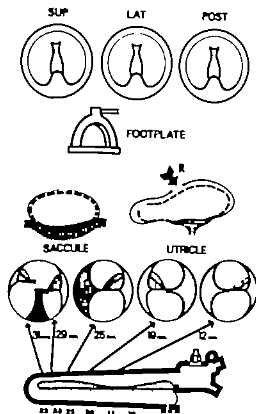
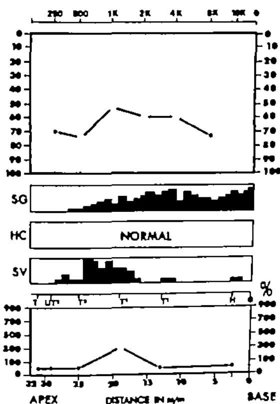


Fig 30

CASE No 4



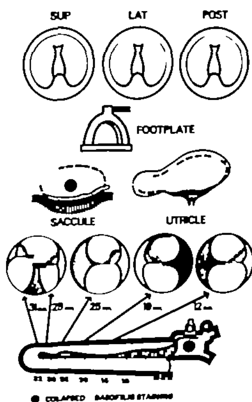
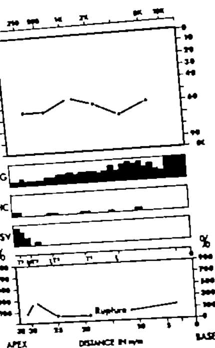


Fig 31

CASE No 5



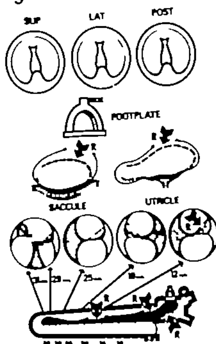


Fig 32

CASE No 6



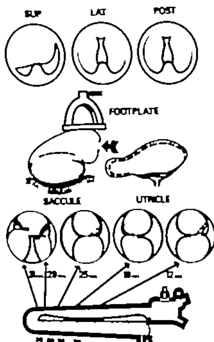
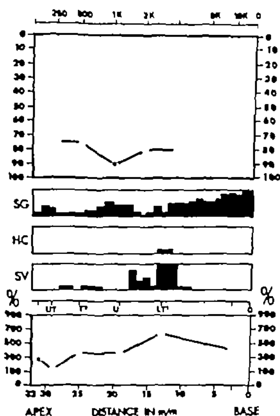


Fig 33 CASE No 7



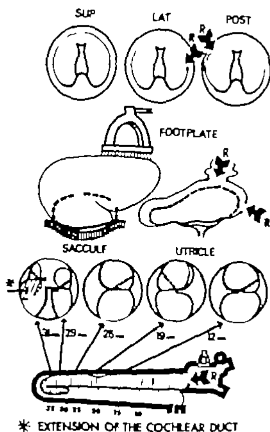
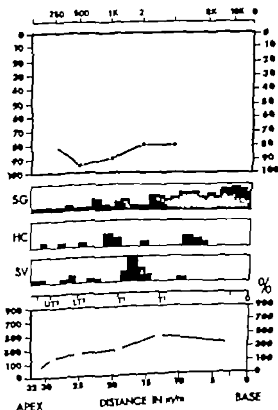


Fig 34 CASE No 8



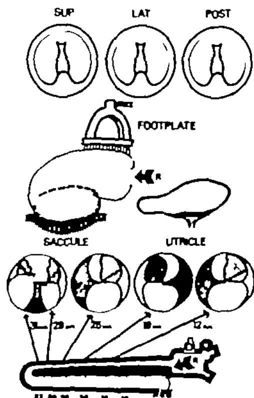
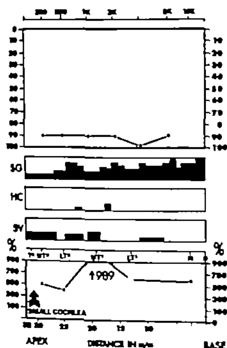


Fig 35 CASE No 9



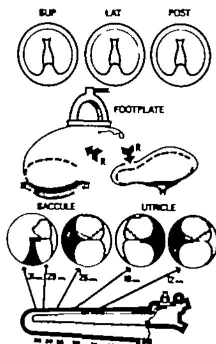
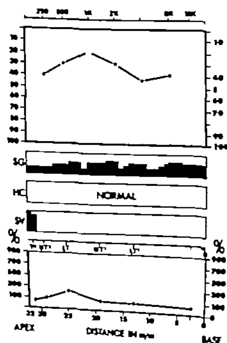


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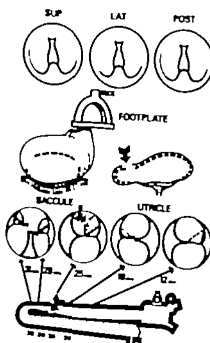
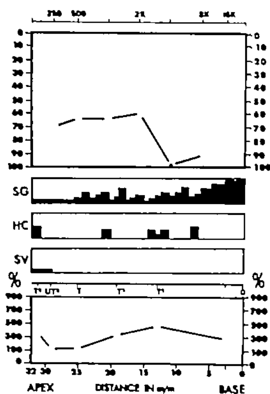


Fig 37

CASE No 11



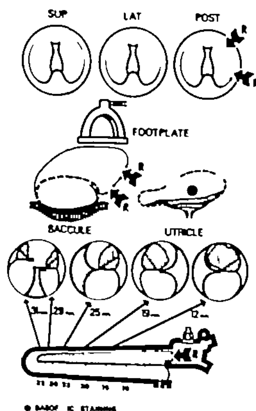
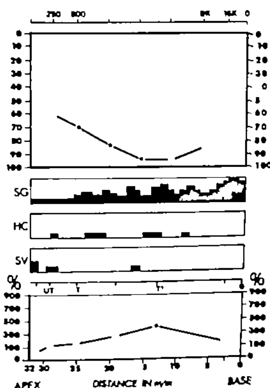


Fig 38

CASE No 12



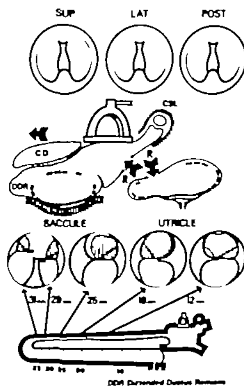
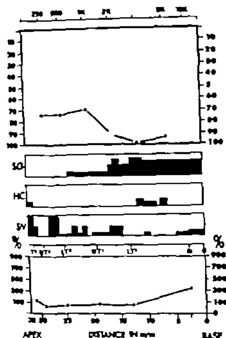


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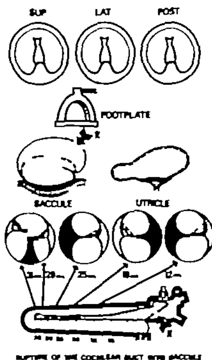
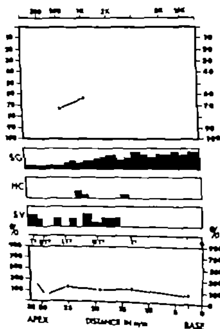


Fig 40 CASE No 14



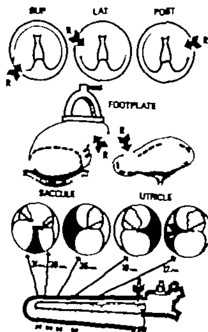
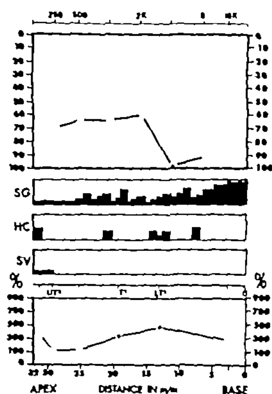


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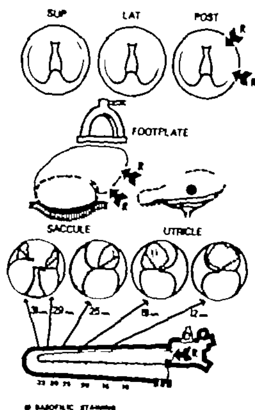
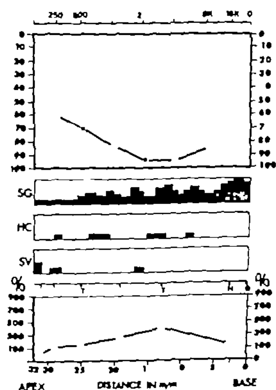


Fig 38 CASE No 12



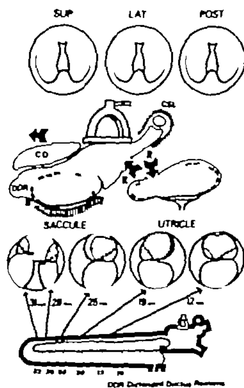
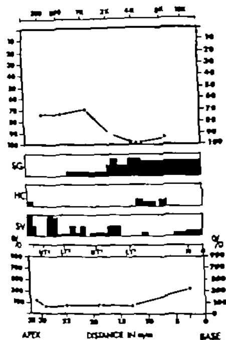


Fig 39 CASE No 13



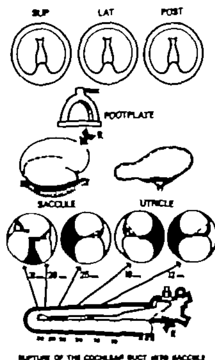
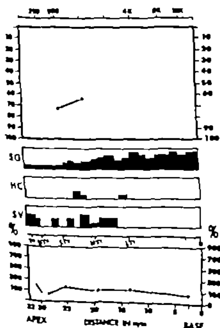


Fig 40 CASE No 14



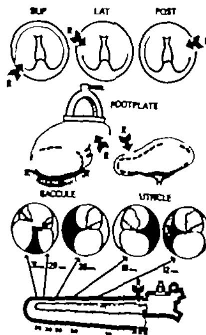
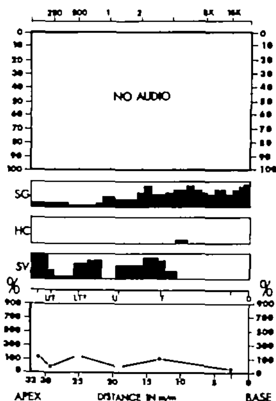


Fig 41

CASE No 15



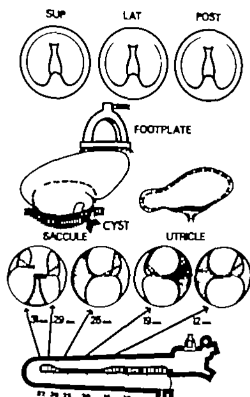
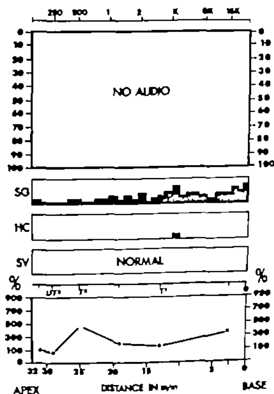


Fig 42

CASE No 16



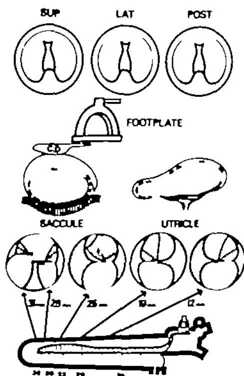
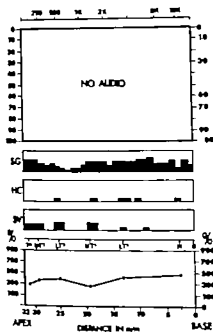


Fig. 43 CASE No 17



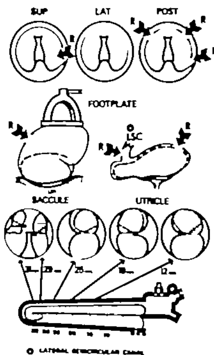
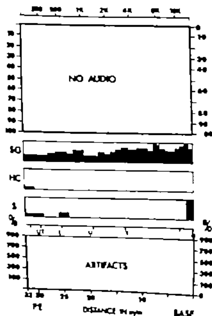


Fig 44 CASE No 18



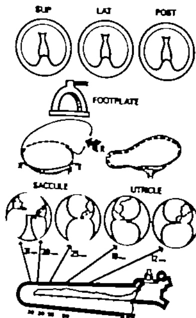
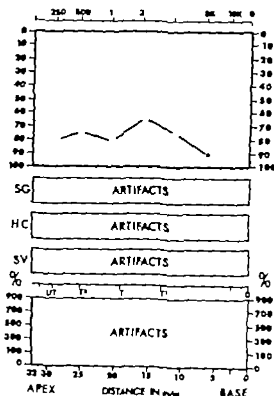
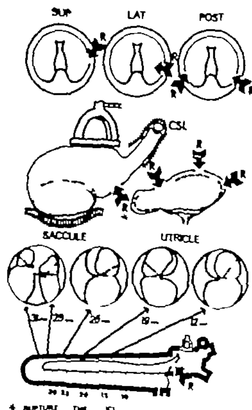


Fig 45 CASE No 19





(19 mm region) LT_2=lower half of the second turn (25 mm region) UT_2=upper half of the second turn (29 mm region) T_3=third turn (31 mm region)

The ordinate shows the percentage increase in area of the cochlear duct in these regions (*see text Volumetric Study*) The lower abscissa indicates distance along the cochlear duct

2. Right diagram

This diagram is a schematic representation of the studied inner ear membranes as seen under light microscopy The black arrows labeled with an "R" appearing in some plates point *to the approximate site of the ruptures The* dotted lines for the utricle and saccule represents an arbitrary normal volume

Summary and Conclusions

This study is based on a detailed examination of the histopathological findings in twenty five temporal bones from twenty individuals *with Meniere s disease*

Interpretation of the findings in human temporal bone pathology is complicated by numerous factors e g postmortem autolysis preparation artifacts coincident pathology long intervals between clinical *evaluation and death of the patient* etc For this reason only consistent findings and definite correlations will be considered

SUMMARY

Histopathologic findings in the labyrinthine membranes

1 *The inferior labyrinth*

Dilatation of the inferior labyrinth is present in varying degrees in all the specimens Hernia-

tion of Reissner's membrane through the helicotrema is found in two specimens (Figs 33 34)

In ten ears the lateral wall of the saccule or the distended ductus reuniens are in contact with the stapes footplate Four of these specimens show a fibrous tissue formation between the membranous wall and the endosteum of the footplate (Fig. 1 2)

The reinforced area of the saccular wall retains its normal position regardless of the degree of distention of the saccule

Definite antemortem collapse of the membranous walls of the cochlear duct are present in two specimens (Figs 5 6 7)

In six out of eight ears with rupture of Reissner's membrane the ruptures are located in the areas of maximum distention Similarly ruptures of the saccular walls are found more frequently in cases of severe or moderate distention than in cases of mild distention.

There is no spatial correlation between the ruptures of Reissner's membrane and the hearing loss Only one ear (Fig. 8) presents pathology at the site of the rupture

2. *The superior labyrinth*

Dilatation of the utricle is mild or absent. Two ears show evidence of antemortem collapse (Figs. 11 and 12)

Two different types of rupture are found in the superior labyrinth The first type (type I) shows a direct communication between the endolymphatic and perilymphatic spaces This type of rupture is only present in the inferior halves of the utricle and the inferior labyrinth

The second type (type II) is characterized by a gap in the normal continuity of the membranous wall sealed by a unicellular replacement membrane Type II ruptures are only found in the semicircular canals and the superior halves of the utricles (Figs. 14 15 16) This type of rupture is most commonly found in the posterior canal ampullae Multiple ruptures of the type II are not infrequent (Fig. 17) and can also be found associated to type I ruptures Some type II ruptures are surrounded by areas of atrophy of the wall (Fig. 18)

The utriculo-endolymphatic valve appears normal or open in all but one specimen (figs 7 10)

3 *Volumetric study*

As previously stated the word "volume" is used to express an estimate of the volume derived from the cross sectional areas of the cochlear spaces at different points along its length

In the cochlea, the average increase in volume of endolymph is computed for two groups one with a hearing loss greater than seventy decibels (db ISO 1964) (N 5) and the other with hearing loss less than seventy decibels (N 7) Comparing the two groups, the volume increase is greater in the group of ears with a hearing loss over 70 db than in the group of ears with a hearing loss under 70 db

The group of ears with a hearing loss less than seventy decibels has a greater volume increase in the apical turn than in the middle and basal turns The group of ears with a hearing loss over seventy decibels has a greater volume increase in the middle and basal turns than in the apical turn (Fig. 21)

The curve obtained by plotting the average percentage of volume increase against the average threshold elevation for the fre quencies 0.25 0.5 1 2, 4 and 8 KHz (Figs 22, 23) shows a definite correlation. This correlation can be seen clearly in bilateral cases where causes of error such as hearing loss due to aging, time lapse following death or errors due to calibration of the audiometers, are minimized (Figs. 22, 23 24)

In the superior labyrinth the measurements included six cases with unilateral Meniere's disease in which the opposite normal sides are available and suitable for study The measurement indicates that the differences between both sides are not significant (Table II)

4 *Cochlear sensory and neural structures*

The hair cell population is normal for age in all specimens This observation relates only to the presence or absence of sensory cells and does not imply that the present cells are functional

There is a ganglion cell loss due to aging The loss is more pronounced in the first 10 mm of the cochlea. This finding is in agreement with previous studies (Otte 1968)

There is a greater percentage of ganglion cell loss in the last 7 mm of the cochlea in the cases of Meniere s disease where the volume increase is over 130% (Table II Fig 25)

There is atrophy of the stria vascularis of varying degrees in all but one of the specimens (Case 16 Fig. 26) In all cases the strial atrophy is more severe in the apical two thirds of the cochlea. There is a striking similarity between the pattern of the atrophy in these specimens and that found in presbycusis (Schuknecht & Ishii 1966 Belal 1974 Schuknecht et al 1974) (Fig 26)

For this reason no attempt has been made to correlate the amount of hydrops with the strial atrophy

CONCLUSIONS

In the interpretation of the histopathological findings in this study we must bear in mind that the morphological changes found at the time of death represent only a stage in the evolution of Meniere s disease To draw any final conclusions with regard to the pathogenesis of Meniere s disease on the basis of these findings would be speculative

However the data obtained from this study suggest that

(1) *There is no clear correlation between* the sensorineural hearing loss and the histopathological findings in the sensory and neural structures

(2) The increase in volume of endolymph is directly related to the hearing loss

In the cases with an average hearing loss less than seventy decibels the temporal bones show a small percentage of increase in endolymph per decibel of hearing loss and the volume increase is more severe in the apical turn than in the middle and basal turns

In the cases with an average hearing loss over seventy decibels the temporal bones show a high percentage of increase in endolymph per decibel of hearing loss and the increase is greater in the middle and basal turns than in the apical turn

(3) There are two different types of ruptures of the membranous walls The "type I" ruptures are of doubtful significance for the following reasons (*a*) They are frequently found in the walls of the inferior labyrinth which are thinner and more distended than the walls of the superior labyrinth and therefore possibly more susceptible to preparation artifact (*b*) They do not show consistent pathological changes at the edges (*c*) Only one temporal bone shows associated pathology in the sensory structures at the site of the rupture

The type II" ruptures are believed to be antemortem for the following reasons (*a*) They show evidence of a reparative process at the edges and a thin replacement membrane seals the discontinuity of the normal wall (*b*) In some instances the edges show evidence of atrophy

The cause of *this* rupture *cannot be* explained solely on the basis of an increase in endolymphatic pressure

It has not been established that the increase in endolymphatic volume reflects an increase in endolymphatic pressure The fact *that two or more* "type II" ruptures are frequently found within the same superior labyrinth would suggest that factors other than an increase in endolymphatic pressure alone are involved in the pathogenesis of this rupture Localized areas of atrophy of the labyrinthine walls could be a factor in causing these ruptures

The protein manifestations of vestibular dysfunction in Meniere s disease may be ex

plained by the varied histopathological findings. Alterations of the physical properties of the labyrinthine membranes e.g. distention, collapse and rupture and possible biochemical changes in the labyrinthine fluids could account for the peripheral vestibular dysfunction It is not possible at this time to assign a particular vestibular symptom to a specific morphological change

Acknowledgements

The author is greatly indebted to Dr Harold F Schuknecht for his encouragement and direction during the study and preparation of this manuscript. Acknowledgement is also due Mr Terrance Bourk for his technical advice in the volumetric study and computer programing and to Mr Robert S Kimura for his advice during this study I also wish to thank Mrs Diane Jones for the preparation of the histopathological material and Ms Elaine Joseph for her help in the preparation of this manuscript.

Permissions

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SUPPLEMENT 339

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AUDITORY
AND EXTRA-AUDITORY EFFECTS

Editor

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— *Nervous and Mental Diseases Clinic*

Prof Bruno Bergamasco Dr Marco Gilli Dr Pietro Benna Dr Anna Maria Covacich Dr Pier Marco Furlan.

— *1st Department of Medical Pathology*

Prof Lorenzo Verdun di Cantogno Dr Riccardo Dallerba Dr Pier Sandro Teagno Dr Leonardo Cocola.

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Prof Giovanni Rossi, M D
Head Department of Audiology
Via Genova 3
10126 Torino
Italy

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URBAN TRAFFIC NOISE
AUDITORY AND EXTRA AUDITORY EFFECTS

Introduction bibliographical survey research aims and technical notes

G Rossi

From the Department of Audiology University of Turin, Turin, Italy

INTRODUCTION

Noise is responsible for four closely linked effects in man These relate to a) hearing b) vegetative functions (cardiocirculatory system, sleep, endocrine performance and the gastro-intestinal apparatus) c) interpersonal relations (state of attention and wakefulness, speech and behaviour) d) overall repercussions on physical and mental activity determined by the degree and type of "disturbance and annoyance" caused by the noise in question. There are, of course, no hard and fast boundaries between these effects. Prolonged interference with sleep, for example, is not without its effect on inter personal relations, to the extent that the "disturbance and annoyance" brought about by ambient noise tends to be exaggerated by a given subject.

Over and above a general statement of this kind, which seeks to stress the limits of this classification, while acknowledging its usefulness, at any rate for illustrative purposes, attention must be given to the relevant literature.

The "Effects of noise on man" have been fully examined over the last twenty years, as a glance at the extensive bibliography compiled by Kryter (1970) in his book on this subject will readily show

Yet the attentive reader will notice that most attention has been directed to the effects of industrial noise. This approach, of course, is fully justified by the noise levels to be found in work environments. In addition, it enables weight to be given to the fact that the contact between men and machines is "enforced" rather than "voluntary"

Voluntary associations between human beings and sources of noise may be discerned solely in the field of individual and communal recreation. Leaving aside situations of this type, the links between man and noise forming an integral part of modern life are not so much the result of "enforcement" as of "unavoidable necessity

Considerations of this kind are of particular importance when dealing with the relation between man and his environment outside working ambients, since here traffic noise is the prime factor In a word, whether we work in quiet or noisy surroundings, we are necessarily subjected to a noisy background.

Two questions may be asked Is this noisy background harmful to health in itself? To what extent are its effects additional to those produced by noise at work? No firm answer can as yet be given. The hesitant opinions expressed in the literature, however show that the matter is one that deserves attention.

BIBLIOGRAPHICAL SURVEY

Effects on hearing

Very few data exist. Lang & Jensen (1967) investigated a possibility of increases in the temporary threshold shift (TTS) in subjects who had driven for 12 hr non-stop TTS changes are dependent on personal factors and appear to be closely linked to the length of exposure to

to have been neglected in the literature. The same appears to be true with respect to changes in cortical evoked potentials.

Work carried out with the most modern and reliable EEG approach to questions related to attention, namely Grey Walter et al.'s Contingent Negative Variation (1964), is also devoid of any reference to the subject.

Changes in verbal communication attributable to traffic noise have also escaped examination, apart from the observations of Robinson (1969) and Beraneck (1954). The former found that a human voice could be clearly heard at a distance of 4 m when the background was not higher than 48 dB(A), while the latter calculated 40-45 dB(A) as the maximum ambient level compatible with the good understanding of radio and TV programmes. Lastly there are no references in the literature to changes in voice emission level in the presence of traffic noise.

RESEARCH AIMS AND TECHNICAL NOTES

The present research was directed to certain features of the effect of traffic noise on hearing, vegetative functions, and interpersonal relations. No attention has as yet been given to overall repercussions in the sense of "disturbance and annoyance" since this varies from one person to another. This side of the matter together with further investigation of the data so far obtained may be looked into later.

Traffic noise tapes were prepared by the G. Ferraris National Electrotechnical Institute, Turin, Italy. The statistical data were processed by the Central Research Department of FIAT's Physical and Mathematical Laboratories. I should like to thank Drs. G. P. Galotto, G. Ruspa, M. Sattin and their assistants.

The following material was examined:

a) ten one-minute recordings of daytime traffic noise, each taken at a different point in Turin
b) the first three recordings from a)
c) a two-hour recording consisting of 12 plays of the material in a)
d) three fifteen-minute recordings of night-time traffic noise, each taken at a different point in Turin and spaced out with a fifteen-minute silent interval
e) an acoustic signal from a Bettendorf reaction meter

The following data were computed for each recording:

1) equivalent sound level (L_{eq}) in dB and dB(A)
2) mean sound level (L_m), in dB and dB(A)
3) standard deviation (σ).

These data were calculated for each minute of the recording in the case of a), for each 10 minutes in the case of c), for each 15 minutes in the case of d). Table 1 gives the overall data picture. Reference is made to the data in

Table 1. *Overall and synthetic data for the urban traffic noise used in the different experiments*

	t	L_m dB	L_{eq} dB	σ dB	L_m dB(A)	L_{eq} dB(A)	σ(A)
	0-10	88.8	89.4	2.35	71.6	73.3	3.54
b	0-3	89.2	89.7	2.30	71.4	72.1	2.40
	0-120	86.8	87.6	3.75	74.1	76.2	4.60
	0-15	63.3	63.6	1.7	53.7	54.7	1.6
	15-30	87.7	89.3	4.1	74.9	76.9	4.3
d	30-45	63.4	63.8	1.6	54	54	0.6
	45-60	86.5	88.7	4.62	71.6	74	4.2
	60-75	63.9	64.2	1.65	54.2	54.2	0.86
	75-90	87.9	90.7	4.5	75.4	77.7	4.45
e	0-1	58.9	59.1	1.05	57.4	57.4	0.60

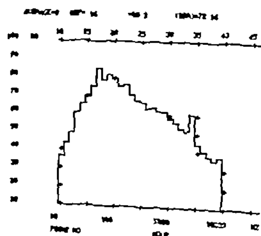


Fig. 1. Sound spectra at one-third of an octave for the 1st minute of tape).

noise and its characteristics. These workers felt that present traffic noise levels do not lead to significant TTS alterations, though they point out that no positive statement can be made since conclusive data are not yet available and the problem requires further investigation

Permanent threshold shift (PTS) changes have been examined only by Llerle & Reger (1958) Occupational deafness depending on the duration of exposure was observed by these workers in the majority of a group of tractor drivers

An equally small amount of attention has been directed to the question of whether the physiological falling-off of hearing with age (presbyacousis) is affected by traffic noise. Wakstein (1968) is of the opinion that such impairment can be accentuated and accelerated by traffic noise, even in subjects with occupational deafness as a result of its continuity

Though some doubts may be cast on the reliability of the personal data collected for their subjects, the findings of Jansen et al (1964), Rosen et al (1962, 1964) and Glorig (1957) are of interest. They showed that the older members of a Sudan tribe, the Mabaan, had distinctly better hearing than persons of the same age in Wisconsin New York Düsseldorf and Cairo whereas those members that had gone to live in Khartoum many years before could hear no better The Mabaan live in surroundings where the average background noise in about 30 dB

Effects on vegetative functions

Thiessen (1969 1970) studied the effect of traffic noise on sleep with recordings of lorries. He found that a mean noise level of 40 dB(A) woke 5 % of his subjects, whereas this figure rose to 30 % at 70 dB(A). Significant EEG signs of a marked fall in the depth of sleep were noted in 10 % and 60 % at these two levels respectively

Schieber et al. (1968) noted that low intensity traffic producing a mean noise level of 60 dB(A) had a much more significant effect on sleep rhythm and characteristics than very heavy traffic at 70 dB(A) It seems, therefore that occasional noise well above the mean background level has a greater effect on sleep than even louder but more continuous noise, presumably as the result of tolerance

Ossipov (1968) has shown that it takes about 1½ hr to get to sleep when traffic noise is 50 dB(A) Deep sleep periods are very short and subjects complain of marked tiredness on waking. He found that 35 dB(A) was an optimum level Twenty minutes was enough to ensure sleep and deep sleep periods lasted 2 2½ hr

Steinecke (1957) came to a similar conclusion though his research was conducted with simulated traffic noise, as did Scott (1972) in his study of EEG changes produced by noise during sleep

Other vegetative functions have received little attention Lang & Jansen (1967) observed increased autonomic system tone on exposure to noise levels comparable to those produced by road traffic. This was accompanied by mydriasis in relation to the intensity of the stimulus and its duration. They suggested that such level could reduce peristalsis and the secretion of saliva and gastric juice, and increase intracranial arterial pressure. These effects may be particularly marked when sudden loud noises are added to the background at irregular intervals Furthermore, Broadbent (1957) asserts that constant repetition of changes in sympathic tone may eventually lead to serious damage to health.

Effects on interpersonal relations

Here attention must first be directed to the modalities of reaction to stimuli of various kinds. One can either take an overall view or else examine the particular significance that given phenomena have in the performance of a reflex activity

As far as " behaviour " is concerned it must be noted that unusual reactions are more commonly attributable to sudden increases in background noise than to any given level No precise data are available for man Hoffmann & Flesher (1963) found that, in animals, reaction intensity is directly proportional to noise peak intensity and apparently unrelated to the intensity of the background noise This means that even the presence of a very high background level does not suffice to increase individual tolerance to sudden very loud noise

Reflex activity in response to light and sound stimuli in the presence of traffic noise appears

to have been neglected in the literature. The same appears to be true with respect to changes in cortical evoked potentials.

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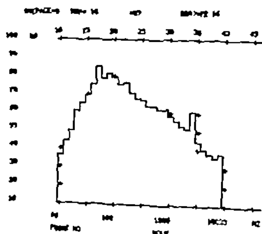


Fig. 1 Sound spectra at one-third of an octave for the 1st minute of tape a).

Fig 2 As last, weighted in accordance with the correction curve in dB(A).

Fig 3 Cumulative distribution of sound level in dB and print-out for the statistical values (1st minute of tape a)

Fig 4 Cumulative distribution of sound levels in dB(A) and print-out for the statistical values (1st minute of tape a).

each paper where the findings are given in L and L_{eq}

Three diagrams were also prepared

1) sound spectra at one third of an octave
2) similar curves weighted in accordance with the correction curve in dB(A)
3) cumulative distribution of the sound level in dB and dB(A)

These diagrams were supplemented with a print-out giving the statistical values L_1, L_{10}, L_{50}, L_{90}. Figs 1-4 show the diagrams for the 1st minute of the tape referred to at a) *supra* by way of example

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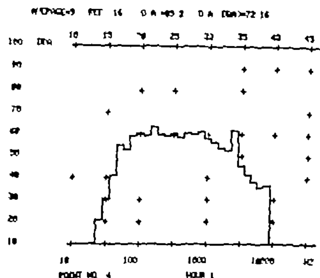


Fig 2 As last, weighted in accordance with the correction curve in dB(A)

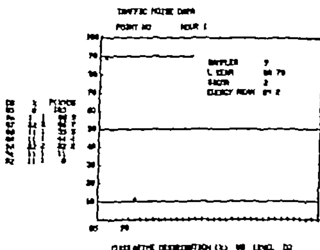


Fig 3 Cumulative distribution of sound level sin dB and print-out for the statistical values (1st minute of tape a).

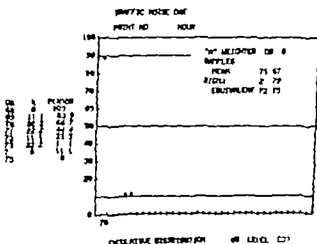


Fig 4 Cumulative distribution of sound levels in dB(A) and print-out for the statistical values (1st minute of tape a).

each paper where the findings are given in L_{50} and L_{eq}

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2) similar curves weighted in accordance with the correction curve in dB(A)
3) cumulative distribution of the sound levels in dB and dB(A)

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TEMPORARY THRESHOLD SHIFT (TTS) DUE TO EXPOSURE TO URBAN TRAFFIC NOISE

G Rossi M Scevola C Magliano

From the Department of Audiology University of Turin Turin Italy

SCOPE OF THE RESEARCH

Our aim was to see whether traffic noise (for details, see the next paragraph) altered the threshold level of the various frequencies of the tonal field and if so to what extent. Evaluation of the threshold is also described in the next paragraph

MATERIAL AND METHODS

Ten subjects of both sexes aged 10-25 yr with no prior history of even slight disease of the auditory apparatus were examined Air and bone thresholds at the frequencies normally employed in audiometry were established for each subject with an Amplifon 300 audiometer before commencing the experiment These were no higher than 5 dB Each subject was then trained in the technical features of the test The right ear was used in 5 subjects and the left ear in the other 5

The experiments were conducted with an automatic Grason-Stadler 1701 audiometer calibrated in HTL. A continuous tone in an ascending fashion was employed The frequency was increased by one octave per minute while intensity was decreased (or increased) at the rate of 2.5 dB per sec The tests were performed in a standard Amplifon G 5 silent booth measuring 240 × 240 × 240 cm itself placed in a room lined with sound absorbing panels.

The tone field (125-8000 Hz) was divided into three 2-octave bands 125-500 Hz 500-2000 Hz 2000-8000 Hz. The mean threshold for the frequencies in each band was obtained by adding the dB values of the bottom peaks in its trace and dividing the result by the number of peaks to two decimal places. Peaks above the 0 dB line were treated as negative and subtracted Computation of the dB value was facilitated by using a special piece of transparent paper with the audiogram 10 dB interval divided into 10 parts

Selection of the dB values for the bottom peaks as opposed to the top peaks or a mean of the two was decided upon after preliminary research (in the press) had shown that the values obtained when the subject presses the button in response to the sound signal are more constant and less subject to variations imposed by attention than those obtained when he no longer hears the sound and releases the button as well as being more constant than values representing the mean between the two

Road noise was taped through a Uher 4400 Report Stereo IC recorder into the circuit of an Amplaid 500 audiometer calibrated in dB SPL, and then to two loudspeakers set 25 cm from each ear of the subject, who was lying on a bed in the booth Before each experiment a Brüel & Kjaer 2209 phonometer fitted with a 1613 octave filter was used to check the intensity of the signal employed as the acoustic signal at the point occupied by the head of the subject

A 2 hr tape compiled by replaying a 10-min recording taken at ten different points in Turin

twelve times was used. Its characteristics were

L_m dB	L_{eq} dB	$\sigma \pm$ dB
87.1	87.8	2.64
L_m dB(A)	L_{eq} dB(A)	$\sigma \pm$ dB(A)
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Following exposure to this road noise at its true intensity for 2 hr the test was repeated, on each subject and on different days, with attenuations of 5 10 15 and 20 dB

Thresholds were determined before each experiment, immediately after exposure to road noise, and 30′ 60′ 90′ and 120′ after the stimulation. Responses were recorded in the form of audiograms written by a Grason-Stadler 1701 X Y recorder connected to the audiometer

TTS was determined for each of the three 2-octave bands, and for each intensity of noise by calculating the difference between the thresholds at 0 30 60 90 and 120 minutes after exposure and the threshold observed before starting the experiment. An overall assessment of TTS behaviour was made by calculating, for each group of 10 values, for each of the 3 bands, and for each time, the mean value of the differences in threshold level with respect to the mean value of the pre-stimulation thresholds and the respective standard deviation (2 σ).

Since a subjective audiometric technique was used in assessing the threshold and its variations, a preliminary check was run to establish the validity of the method. For this purpose, a basal threshold was determined for each of the ten subjects and its variations over the experimental time period in the absence of road noise were noted, the aim being to see how far the threshold for each frequency band changed as a result of wearing the earphones or due to simple tiredness brought about by the length of the experiment.

The mean difference between the threshold levels observed at the start of the test and during this time period was calculated for each set of 10 data, plus the standard deviation (σ). This gave a normal variation range for each frequency band and for each time period (shown by the dark bands in figs. 1 2 & 3). Values falling outside these limits could thus be considered as attributable to the acoustic stimulation.

RESULTS

Our overall results are illustrated in Table 1 and figs. 1 3 Mean TTS values were divided into three groups 1) means (with S D) that were outside the normal range in 100 % of cases 2) means (with S.D) that were outside the normal range in at least 50 % of cases 3) means (with S.D) that were outside the normal range in less than 50 % of cases.

TTS behaviour *in relation to intensity* was examined first. It was found that values for the 125-500 Hz range fell into Group 1 when traffic noise was supplied at its real intensity as well as with attenuations of 5 dB and 10 dB, Group 3 values were obtained with attenuations of 15 dB and 20 dB

In the case of the 500-2000 Hz band, real intensity alone gave Group 1 values. Attenuations of 5 dB and 10 dB and of 15 dB and 20 dB gave Group 2 and Group 3 values respectively

Lastly real intensity and attenuations of 5 dB and 10 dB produced Group 2 values in the case of the 2000-8000 Hz band, whereas attenuations of 15 dB and 20 dB led to Group 3 values.

Assessment of TTS *in function of the time elapsed from the cessation of acoustic stimulation* showed that Group 1 in the case of the 125-500 and 500-2000 Hz bands values were obtained when traffic noise was supplied at its real intensity with Group 2 values for the 2000-8000 Hz band. Return to the normal range was observed within 90′ 120′ and 60′ for the three bands respectively following cessation of the stimulus.

Attenuation of 5 dB gave Group 1 values for the first frequency band and Group 2 values for the remainder Recovery times were 60′ for the first two bands and 30′ for the third.

Attenuation of 10 dB resulted in Group 1 values for the first band only with Group 2 values for the other two bands. Recovery occurred after 30′ in all three cases.

Attenuation of 15 dB gave Group 2 values for the first band only with a recovery time of 30′ In the case of the other two bands, TTS values already lay within the normal range at the end of the exposure to traffic noise. This was true for all three bands when an attenuation of 20 dB was applied.

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74.6	76.8	4.73

Following exposure to this road noise at its true intensity for 2 hr the test was repeated, on each subject and on different days, with attenuations of 5 10, 15 and 20 dB

Thresholds were determined before each experiment, immediately after exposure to road noise, and 30′ 60′ 90′ and 120′ after the stimulation. Responses were recorded in the form of audiograms written by a Grason-Stadler 1701 X Y recorder connected to the audiometer

TTS was determined for each of the three 2-octave bands, and for each intensity of noise by calculating the difference between the thresholds at 0, 30, 60 90 and 120 minutes after exposure and the threshold observed before starting the experiment. An overall assessment of TTS behaviour was made by calculating, for each group of 10 values, for each of the 3 bands, and for each time, the mean value of the differences in threshold level with respect to the mean value of the pre-stimulation thresholds and the respective standard deviation (2 σ).

Since a subjective audiometric technique was used in assessing the threshold and its variations, a preliminary check was run to establish the validity of the method. For this purpose, a basal threshold was determined for each of the ten subjects and its variations over the experimental time period in the absence of road noise were noted, the aim being to see how far the threshold for each frequency band changed as a result of wearing the earphones or due to simple tiredness brought about by the length of the experiment.

The mean difference between the threshold levels observed at the start of the test and during this time period was calculated for each set of 10 data, plus the standard deviation (2). This gave a normal variation range for each frequency band and for each time period (shown by the dark bands in figs. 1 2 & 3). Values falling outside these limits could thus be considered as attributable to the acoustic stimulation.

RESULTS

Our overall results are illustrated in Table 1 and figs. 1 3. Mean TTS values were divided into three groups 1) means (with S.D) that were outside the normal range in 100 / of cases 2) means (with S.D) that were outside the normal range in at least 50 / of cases 3) means (with S D) that were outside the normal range in less than 50 / of cases.

TTS behaviour *in relation to intensity* was examined first. It was found that values for the 125-500 Hz range fell into Group 1 when traffic noise was supplied at its real intensity as well as with attenuations of 5 dB and 10 dB, Group 3 values were obtained with attenuations of 15 dB and 20 dB

In the case of the 500-2000 Hz band, real intensity alone gave Group 1 values. Attenuations of 5 dB and 10 dB and of 15 dB and 20 dB gave Group 2 and Group 3 values respectively

Lastly real intensity and attenuations of 5 dB and 10 dB produced Group 2 values in the case of the 2000-8000 Hz band, whereas attenuations of 15 dB and 20 dB led to Group 3 values.

Assessment of TTS *in function of the time elapsed from the cessation of acoustic stimulation* showed that Group 1 in the case of the 125-500 and 500-2000 Hz bands values were obtained when traffic noise was supplied at its real intensity with Group 2 values for the 2000-8000 Hz band. Return to the normal range was observed within 90′ 120′ and 60′ for the three bands respectively following cessation of the stimulus.

Attenuation of 5 dB gave Group 1 values for the first frequency band and Group 2 values for the remainder Recovery times were 60 for the first two bands and 30′ for the third.

Attenuation of 10 dB resulted in Group 1 values for the first band only with Group 2 values for the other two bands. Recovery occurred after 30′ in all three cases.

Attenuation of 15 dB gave Group 2 values for the first band only with a recovery time of 30′ In the case of the other two bands, TTS values already lay within the normal range at the end of the exposure to traffic noise. This was true for all three bands when an attenuation of 20 dB was applied.

Table 1 *TTS behaviour following exposure to road noise for 120 Mean overall evaluation of data from 10 subjects*

Time elapsed after cessation of road noise	Band 125 Hz − 500 Hz	Band 500 Hz − 2000 Hz	Band 2000 Hz − 8000 Hz	Intensity of road noise
0	+ 7 47 ± 3. 6	+ 7 83 ± 6.06	+ 4.90 ± 4.5?	Real intensity
30	+ 4.20 ± 6.0_	+ 3.36 ± _16	+ 3 00 ± 5.38	
60	+ 3 04 ± 3.30	+ _59 ± 4._4	+ 0.94 ± 4 60	
90	+ 0.50 ± 4.23	+ 1.36 ± 4.36	+ 0.43 ± _56	
120	− 0.14 ± 3 06	− 0 1 ± 1 72	+ 0.16 ± 1.80	
0	+ 5.39 ± 3.23	+ 4._1 ± 4.80	− _83 ± _96	5 dB attenuation
30	− _90 ± _68	+ 1 78 ± 4.36	− 1.30 ± 3 08	
60	+ 0.64 ± 1 76	+ 0.74 ± _58	− 0.14 ± _90	
90	− 0.36 ± 1.38	− 0.05 ± _64	− 0.41 ± 1.39	
120	+ 0.08 ± 0.67	− 0.01 ± 1.28	− 0.30 ± 0.55	
0	+ 4 11 ± _40	− _13 ± _00	+ 1 6_ ± _94	10 dB attenuation
30	− 1 04 ± 3.7?	− 0.85 ± 2.04	+ 0.30 ± _60	
60	+ 0 46 ± 4 06	+ 0._1 ± 2.06	+ 0.20 ± 1.28	
90	− 0.25 ± 2.36	0 ± 1 18	− 0 04 ± 0.88	
120	+ 0 13 ± 1 14	− 0 19 ± 0. 4	+ 0 15 ± 1.26	
0	+ 0 67 ± _84	− 0.69 ± 1 40	+ 0 40 ± 1 60	15 dB attenuation
30	− 0.27 ± 1 60	− 0.05 ± 1.94	+ 0._3 ± 1 8	
60	+ 0 49 ± 1 4	+ 0.33 ± 1.5	− 0 19 ± _06	
90	+ 0.34 ± 1 06	+ 0.3 ± 1.28	− 0.29 ± 0.56	
120	− 0 40 ± 1 0	− 0._ ± 1.28	− 0.28 ± 1.28	
0	+ 0.35 ± 1 1	− 0.27 ± _00	− 0.20 ± 0.88	20 dB attenuation
30	+ 0.34 ± 1.96	− 0 15 ± 1.8_	− 0.34 ± 1 88	
60	+ 0.37 ± 1 06	− 0.01 ± 1 68	+ 0.14 ± 1.36	
90	− 0.20 ± 1 00	+ 0 46 ± 1.38	− 0 18 ± 1 00	
120	− 0 15 ± 0 9	− 0.10 ± 1.5	− 0.29 ± 1.3	

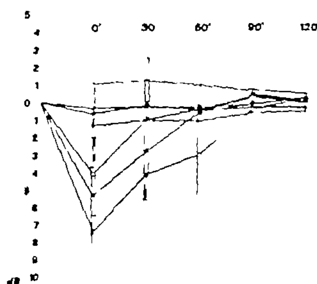


Fig 1 TTS behaviour following exposure to road noise for 120 Mean overall evaluation of data from 10 subjects for the 125-500 Hz band ——□—— real intensity ——•—— 5 dB attenuation ———— 10 dB attenuation ——+—— 15 dB attenuation ——*—— 20 dB attenuation.

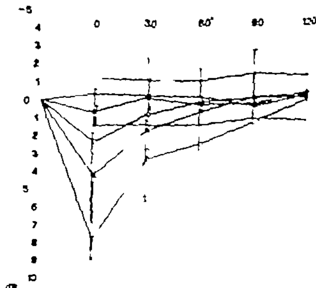


Fig TTS behaviour following exposure to road noise for 120 Mean overall evaluation of data from 10 subject for the 500-2000 Hz band ———— real intensity ——•—— 5 dB attenuation ———— 10 dB attenuation ——+—— 15 dB attenuation ——*—— 20 dB attenuation

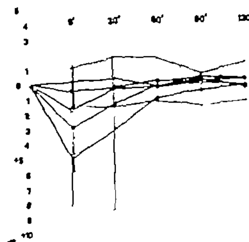


Fig. 3. TTS behaviour following exposure to road noise for 120′. Mean overall evaluation of data from 10 subjects for the 2000-8000 Hz band. ——□—— real intensity ——•—— 5 dB attenuation ——△—— 10 dB attenuation ——+—— 15 dB attenuation ——*—— 20 dB attenuation.

CONCLUSIONS

With reference to the features of the noise employed, its duration, and the method used to evaluate TTS, our results make it clear that exposure to real traffic noise leads to a mean TTS shift of about 7 dB for frequencies of 125 to 2000 Hz, with recovery times of 90′ in the case of the 125-500 Hz band and 120′ for the 500-2000 Hz band. A shift of about 5 dB and a recovery time of 60′ were noted for the 2000-8000 Hz band.

Attenuation of 5 dB resulted in a shift of about 5, 4 and 3 dB respectively for the three frequencies, followed by recovery times of 60′, 60′ and 30′. Attenuation of 10 dB led to shifts of about 4 dB, 2 dB and 2 dB, with recovery after 30′ in all three cases.

15 dB and 20 dB attenuations meant that traffic noise failed to move TTS outside its normal spectrum of variation in the absence of acoustic stimulation.

Mean TTS following exposure to real road noise was slightly higher in the case of the 500-2000 Hz band, as opposed to the 125-500 Hz band, with recovery times of 120′ and 90′ respectively. For the 2000-8000 Hz band, mean TTS was lower than it was in the case of the other two bands, with a recovery time of 60′.

Bearing in mind the spectrum of the traffic noise employed and the well known features of TTS behaviour, our results appear to substantiate the *significance* of a hypothesis that could have been validly postulated in the first instance.

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CHANGES IN STAPEDIUS REFLEX AMPLITUDE AND LATENCY FOLLOWING EXPOSURE TO URBAN TRAFFIC NOISE

G Rossi P Solero M Penna

From the Department of Audiology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

Bearing in mind what has so far been discovered with reference to the reflex dynamics of the stapedius, and the views put forward concerning its function an examination was made of changes in stapedius maximum contraction latency and amplitude due to fatigue produced by exposure to traffic noise for 3 minutes

It was felt that the results of the research might be of some assistance in determining the part played by the stapedius in protecting the inner ear from loud prolonged sounds.

MATERIAL AND METHODS

Seven subjects aged 19-26 yr with no history of diseases of the ear were examined Air and bone thresholds at the frequencies normally employed in audiometry were established for each subject before commencing the experiment An Amplifon 300 audiometer was used for this purpose and the right and left ear were tested in 4 and 3 subjects respectively in a silent room lined with sound-absorbing panels Thresholds were no higher than 5 dB

Comparison was made between changes in latency and amplitude of the maximum contraction of the stapedius, before and after exposure to traffic noise for 3 min and at 2 intervals for 10 subsequently

A tape consisting of three 1 minute recordings of daytime noise taken at different points of Turin was used Its characteristics were

L_m dB	L_{eq} dB	σ + dB
89 2	89 7	2.3
L_m dB(A)	L_{eq} dB(A)	σ + dB(A)
71 4	71 1	2 4

This noise was fed through a Uher 4400 stereo I C recorder into the circuit of an Amplaid 500 audiometer calibrated in dB SPL, and into the headphone worn by the subject via an Amplaid Z impedance meter

Stapedius maximum contraction amplitude and latency and the changes in these parameters brought about by traffic noise were evaluated with the aid of a pure 1000 Hz tone at 100 dB lasting 1 sec. Since the stapedius reflex usually occurs in response to sounds 70-75 dB higher than the threshold of the pure tone employed as stimulus, an intensity value of 100 dB was used to ensure that the response obtained before exposure to noise would be of sufficient amplitude to allow the changes induced by muscle fatigue to be reliably determined

Amplitude was recorded on graph paper (in mm) by means of an X Y Grason-Stadler recorder connected to the impedance meter At the same time, latency was evaluated in msec by inserting the pure tone and the response into the circuit of a 5103 N Tektronix oscilloscope calibrated at 200 msec, followed by photographic recording with a Polaroid Tektronix C_4 oscilloscope camera. Amplitude was arbitrarily measured in mm For greater ac

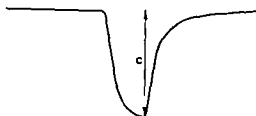


Fig. 1 a) time elapsed between presentation of the stimulus and beginning of reflex contraction of the stapedius b) latency of maximum contraction c) amplitude of maximum contraction.

curacy the graphs were enlarged 10 times with a Plawa epidiascope and values were read with a ruler gratuated in mm (fig. 1).

Amplitude and latency were evaluated immediately prior to exposure. At the end of the exposure (3'), the pure tone was immediately switched through to the subject's ear and then again at 2' intervals.

Following exposure to traffic noise at its true intensity each subject heard the same recording on different days with an attenuation of 5 10 15 20 and 25 dB. Noise intensity was determined with a Brüel & Kjaer 2209 phonometer fitted with a 1613 octave filter before the commencement of each experiment.

Before and after exposure to real or attenuated traffic noise, and at the end of each experiment, drumhead compliance in the absence of the reflex was evaluated with an intracavity pressure of 200 mm H_2O. A tympanometric curve was also elaborated on each occasion to assess the give in the absence of the reflex and with the membrane slack. The values obtained were in all cases the same as those observed before exposure to noise.

Both before and at the end of each experiment, a linear relationship was always noted between the volumetric variations of a perfectly sealed tester calibrated in cm³ and the shift amplitude of the pen connected to the impedance meter. This check on the percent evaluation of changes in stapedius contraction latency and amplitude after exposure to noise was rendered necessary by the observation that these parameters were not identical in the tested subjects before exposure.

The method employed was checked before commencing the experiment to assess individual variations in stapedius response in function of the proposed time pattern in the absence of noise. Since the biological phenomenon involved could well be affected by extraneous influences of undetermined entity variations of some kind were, indeed, to be expected.

A stapedius reflex was therefore elicited from each subject in the absence of traffic noise on 3 occasions, on 3 successive days, using the proposed experimental pattern initially after 3

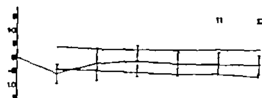


Fig. 2. Latency of maximum stapedius contraction following exposure to unattenuated traffic noise. This and the remaining figures show mean values and standard deviation (2 σ) for 7 subjects. The dark band shows the normal range of variation for these subjects in the absence of traffic noise.

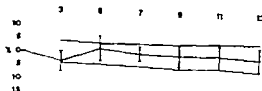


Fig. 3 As last, with attenuation of 5 dB.

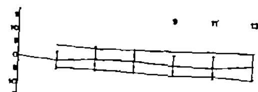


Fig. 4 As last, with attenuation of 10 dB.

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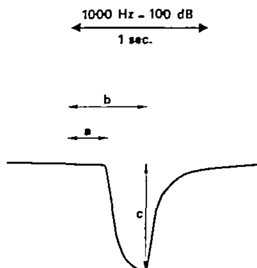


Fig. 1. a) time elapsed between presentation of the stimulus and beginning of reflex contraction of the stapedius. b) latency of maximum contraction. c) amplitude of maximum contraction.

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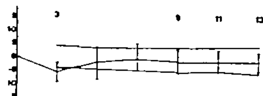


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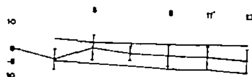


Fig. 3. As last, with attenuation of 5 dB.

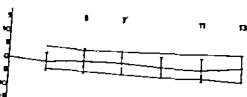


Fig. 4. As last, with attenuation of 10 dB.

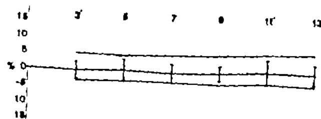


Fig 5 As last, with attenuation of 15 dB.

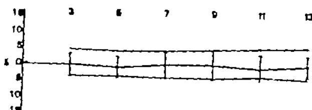


Fig 6 As last with attenuation of 20 dB.

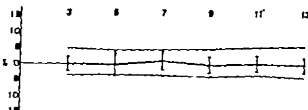


Fig 7 As last, with attenuation of 25 dB.

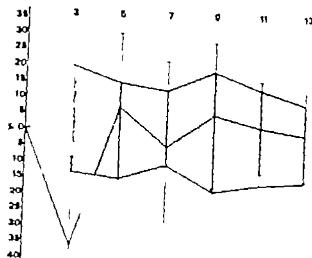


Fig 8 Amplitude of maximum stapedius contraction following exposure to unattenuated traffic noise. For details, see fig. _

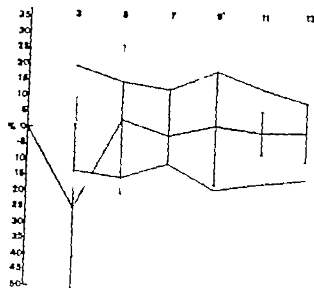


Fig 9 As last, with attenuation of 5 dB

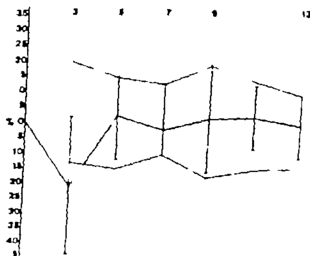


Fig 10 As last, with attenuation of 10 dB

and then at 2 intervals for 10 Latency and amplitude were determined on each occasion.

The mean findings and their standard deviation (2 σ) were used to establish the normal variation ranges for these 7 subjects at each experimental time (shown as dark bands in figs. 2 13)

RESULTS

These are illustrated in figs. 2 to 13 Values obtained before exposure to noise obviously differed from one subject to another Absolute individual and overall variations were clearly of no assistance in evaluating the phenomenon under examination and use was therefore made of percent only so that a reliable and meaningful point of comparison could be obtained

Percent changes in amplitude and latency were referred to the overall values for these parameters, i e the means (and 2 σ) determined before the test.

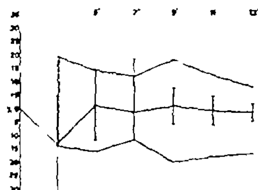


Fig. 11 As last, with attenuation of 15 dB.

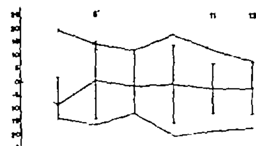


Fig. 12. As last, with attenuation of 20 dB.

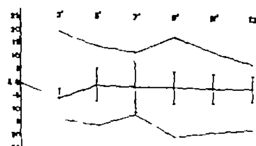


Fig. 13 As last, with attenuation of 25 dB

The data were classified with reference to 3 groups

Group 1 mean values with standard deviation that exceeded the normal variation range in all cases

Group 2 mean values with standard deviation that exceeded the normal variation range in at least 50 of cases

Group 3 mean values with standard deviation that exceeded the normal variation range in less than 50 of cases.

In the case of *latency of maximum contraction of the stapedius* exposure to traffic noise for 3 at its true intensity led to a mean per cent reduction of 5.32 ± 3.44 msec. In more than 50 of cases, this reduction exceeded the normal variation range. At the end of the first three 2' intervals, this pattern was unchanged. At the 11th and 13th minutes, normalisation was apparent. There were no Group 1 values.

An attenuation of 5 dB in noise intensity was accompanied by Group 3 values after 3 and 5' followed by normalisation. Further decibel reductions led to further Group 3 values. In most cases, indeed, these were within the normal range.

Exposure for 3 to unattenuated traffic noise was followed by Group 2 values and a mean percent reduction of 36.01 ± 27.36 in *amplitude of maximum contraction of the stapedius* This pattern persisted until the 9th minute, followed by normalisation.

An attenuation of 5 dB again led to Group 2 values after 3 After 5 and 7' values were in Group 3 Values falling within the normal range were noted at 11 and 13

Values were in Group 2 after 3 with an attenuation of 10 dB After 5 percent variations within the normal range appeared, whereas mean values were in Group 3 after 7' and 9 and within the normal range after 11 and 13

A reduction of 15 dB led to Group 3 values after 3 and 7' with percent variations within the normal range at the 5th, 9th, 11th and 13th minutes.

Apart from Group 3 values after 7' with 20 dB attenuation, percent changes were within the limits of normal at all times when the *intensity* of traffic noise was reduced by 20 dB and 25 dB.

It will be seen that no *Group 1* mean values were observed under any of the experimental conditions.

CONCLUSIONS

In the case of *amplitude of maximum contraction of the stapedius* our results make it clear that this parameter varies over an extremely wide range, even under normal conditions, i.e. in the absence of fatigue caused by *traffic noise*. Stress may be laid on this fact, since it offers real

evidence of a phenomenon whose features and meaning are not fully established. Suffice it to recall here that reflex contraction of the stapedius cannot even be detected in about 1 of subjects, that some persons can contract the muscle voluntarily (Moller 1974), and that the characteristics of contraction itself would appear to be related to attention (Brasher et al., 1969)

Exposure to real traffic noise leads to an approximately 36 / reduction in amplitude after 3 Attenuation by stages is followed by a gradual fall in this figure. A reduction of 20 and 25 dB in fact, results in the observation of values falling within the normal range.

The situation immediately after the 3 exposure period is of interest, as it is marked by a rebound. At the end of the first 2 period of silence, i.e. 5 after the start of the experiment, the reduction in amplitude is less than that at 7 irrespective of whether real or attenuated traffic noise is employed Subsequently the return to normal values is a direct function of the degree of attenuation employed This means that while fatigue is at its maximum after 3 and can even be induced when traffic noise is diminished by 15 dB, its subsequent elimination is not linear but is marked by a rebound from nearly normal values to levels that are, however a long way from those observed at the end of the 3 exposure period

Turning now to *latency of maximum contraction of the stapedius* our findings show that exposure to traffic noise at its real intensity for 3 is responsible for a mean reduction of about 5 /. Attenuation of 5 dB is accompanied by the same result though the percent incidence is less. Return to what may be considered the normal range of variation occurs quickly and appears devoid of linearity at least under our experimental conditions.

Depressed latency values, on the other hand, may be more apparent than real, since they may be a direct expression of the reduction in amplitude induced by fatigue. Indeed, no statistically significant difference in values was noted after exposure to traffic noise in the *time elapsed between presentation of the stimulus and the beginning of reflex contraction of the stapedius* Virtually the same data were constantly observed for each subject and need not be set out in detail here. It may well be that reduction in latency of maximum contraction is entirely dependent on reduction in amplitude. The former however falls by only 5 , as against the 36 drop in amplitude. This in itself is enough to show that the maximum contraction of the fatigued muscle, albeit reduced in amplitude, is reached almost as quickly as under normal conditions. Changes in amplitude and latency times of the maximum contraction of the stapedius may offer a guide to the effectiveness of the protection thought to be given to the inner ear by the stapedius muscle in normal situations and after exposure to fatiguing noise.

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CHANGES IN THE TIME OF REACTION TO LIGHT AND SOUND SIGNALS IN THE PRESENCE OF URBAN TRAFFIC NOISE

G Rossi C Magliano M Scevola

From the Department of Audiology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

Motor activity takes place via pre-established nervous pathways that can translate into movement a response or reaction to a stimulus received by the sensory organs.

The time required to react to a given stimulus may be affected by attention, habituation and fatigue. A competitive stimulus of the same nature as the first may also have the same effect on the complex mechanism triggering the reaction. Both signals use the same nervous pathways to reach the central system Interference with the performance of motor activity following reception of the meaningful signal is inevitable.

A situation of this kind occurs every time a motor activity in response to an acoustic signal is required in noisy surroundings. Traffic noise is an example of a competitive stimulus. The almost continuous interference that it creates is an important object of study

In this connection, a useful comparison can be made with the pattern followed by motor reaction time in response to a light signal, since this employs a different route to noise on its path to the central system. No interference should therefore take place between a significant (*light*) and a competitive (traffic noise) stimulus in such conditions.

This paper investigates changes in the reaction time required for the performance of a simple and a complicated movement following a light or an acoustic stimulus presented at the same time as road noise.

MATERIAL AND METHODS

Ten subjects aged 20-25 yr with normal hearing and no history of auditory disease were used.

Air and bone thresholds at the frequencies normally employed in audiometry were established for each subject with an Amplifon 300 audiometer before commencing the experiment thresholds were no higher than 5 dB. The experiment was done with the subject lying on a bed inside a standard Amplifon G 5 silent booth measuring 240 × 240 × 240 cm with soft lighting. This booth was placed in a room lined with sound-absorbing panels. Reaction times in the presence of traffic noise were evaluated with respect to a light and an acoustic stimulus supplied by a cassette connected to an original Bettendorf reaction meter calibrated in centiseconds. In the case of the light stimulus, the cassette was placed on the wall in front of the subject s head and about 2 m from his eyes. For the acoustic stimulus, the cassette was set behind the head, 10 cm above its vertex and 30 cm from each ear A recording taken at the place occupied by each ear showed the sound signal to have the following characteristics

L_m dB	L_{eq} dB	$\sigma +$ dB
58.9	59 05	1 04
L_m dB(A)	L_{eq} dB(A)	$\sigma +$ dB(A)
57 4	57.4	0 60

On the appearance of either the light or the sound signal, the subject was required to move his right hand to break a ray of light striking

evidence of a phenomenon whose features and meaning are not fully established Suffice it to recall here that reflex contraction of the stapedius cannot even be detected in about 1% of subjects, that some persons can contract the muscle voluntarily (Møller 1974) and that the characteristics of contraction itself would appear to be related to attention (Brasher et al., 1969)

Exposure to real traffic noise leads to an *approximately 36% reduction in amplitude after 3* Attenuation by stages is followed by a gradual fall in this figure A reduction of 20 and 25 dB in fact, results in the observation of values falling within the normal range.

The situation immediately after the 3 exposure period is of interest, as it is marked by a rebound. At the end of the first 2 period of silence, i e 5 after the start of the experiment, the reduction in amplitude is less than that at 7 irrespective of whether real or attenuated traffic noise is employed Subsequently the return to normal values is a direct function of the degree of attenuation employed This means that, while fatigue is at its maximum after 3 and can even be induced when traffic noise is diminished by 15 dB its subsequent elimination is not linear but is marked by a rebound from nearly normal values to levels that are, however a long way from those observed at the end of the 3 exposure period

Turning now to *latency of maximum contraction of the stapedius* our findings show that exposure to traffic noise at its real intensity for 3 is responsible for a mean reduction of about 5% Attenuation of 5 dB is accompanied by the same result, though the percent incidence is less Return to what may be considered the normal range of variation occurs quickly and appears devoid of linearity at least under our experimental conditions

Depressed latency values, on the other hand, may be more apparent than real, since they may be a direct expression of the reduction in amplitude induced by fatigue Indeed, no statistically significant difference in values was noted after exposure to traffic noise in the *time elapsed between presentation of the stimulus and the beginning of reflex contraction of the stapedius* Virtually the same data were constantly observed for each subject and need not be set out in detail here It may well be that reduction in latency of maximum contraction is entirely dependent on reduction in amplitude The former however falls by only 5% as against the 36% drop in amplitude This in itself is enough to show that the maximum contraction of the fatigued muscle, albeit reduced in amplitude is reached almost as quickly as under normal conditions Changes in amplitude and latency times of the maximum contraction of the stapedius may offer a guide to the effectiveness of the protection thought to be given to the inner ear by the stapedius muscle in normal situations and after exposure to fatiguing noise

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CHANGES IN THE TIME OF REACTION TO LIGHT AND SOUND SIGNALS IN THE PRESENCE OF URBAN TRAFFIC NOISE

G Rossi, C. Magliano M Scevola

From the Department of Audiology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

Motor activity takes place via pre-established nervous pathways that can translate into movement a response or reaction to a stimulus received by the sensory organs.

The time required to react to a given stimulus may be affected by attention, habituation and fatigue. A competitive stimulus of the same nature as the first may also have the same effect on the complex mechanism triggering the reaction. Both signals use the same nervous pathways to reach the central system. Interference with the performance of motor activity following reception of the meaningful signal is inevitable

A situation of this kind occurs every time a motor activity in response to an acoustic signal is required in noisy surroundings. Traffic noise is an example of a competitive stimulus. The almost continuous interference that it creates is an important object of study

In this connection, a useful comparison can be made with the pattern followed by motor reaction time in response to a light signal, since this employs a different route to noise on its path to the central system. No interference should therefore take place between a significant (light) and a competitive (traffic noise) stimulus in such conditions.

This paper investigates changes in the reaction time required for the performance of a simple and a complicated movement following a light or an acoustic stimulus presented at the same time as road noise.

MATERIAL AND METHODS

Ten subjects aged 20-25 yr with normal hearing and no history of auditory disease were used.

Air and bone thresholds at the frequencies normally employed in audiometry were established for each subject with an Amplifon 300 audiometer before commencing the experiment thresholds were no higher than 5 dB The experiment was done with the subject lying on a bed inside a standard Amplifon G 5 silent booth measuring 240 × 240 × 40 cm with soft lighting. This booth was placed in a room lined with sound-absorbing panels. Reaction times in the presence of traffic noise were evaluated with respect to a light and an acoustic stimulus supplied by a cassette connected to an original Bettendorf reaction meter calibrated in centiseconds. In the case of the light stimulus, the cassette was placed on the wall in front of the subject's head and about 2 m from his eyes. For the acoustic stimulus, the cassette was set behind the head, 10 cm above its vertex and 30 cm from each ear A recording taken at the place occupied by each ear showed the sound signal to have the following characteristics

L_m dB	L_{eq} dB	$\sigma \pm$ dB
58.9	59.05	1.04
L_m dB(A)	L_{eq} dB(A)	$\sigma \pm$ dB(A)
57.4	57.4	0.60

On the appearance of either the light or the sound signal, the subject was required to move his right hand to break a ray of light striking

a photoelectric cell directly connected to the reaction meter

Two types of motor reaction were investigated a simple reaction and a complicated reaction In the first case, the subject lay on the bed with his right arm extended along his side and his fingers outstretched The reaction required was a simple flexion of the forearm without moving the elbow The tips of the fingers cut the ray of light passing above and across the subject at the top of their arc. Fifty stimuli were supplied in 3 at randomised intervals to prevent habituation

The same procedure was followed for the complicated reaction In this case, however the subject s hand had to touch his left shoulder the light ray ran paralled to his left flank and was cut when the fingertips began their descent towards the shoulder

Road noise was supplied by means of a tape consisting of three 1 minute recordings taken at different points of Turin Its characteristics were

L_m dB	L_{eq} dB	$\sigma +$ dB
89 2	89 7	2.3
L_m dB(A)	L_{eq} dB(A)	$\sigma +$ dB(A)
71 4	72.1	2.4

This noise was fed through a Uher 4400 stereo I C recorder to the circuit of an Amplaid 500 audiometer calibrated in dB SPL, and then to two loudspeakers set 25 cm from each ear Before commencing each experiment, a Brüel & Kjaer 2209 phonometer fitted with a 1613 octave filter was used to check the intensity of the traffic noise at the height of each ear

Following exposure to road noise at its true intensity attenuations of 5 10, 15 and 20 dB were introduced A series of 50 tests occupying 3 was run at intervals of 3 (with the subject at rest on the bed) for each intensity level The arithmetic mean of each set of 50 values was used as the mean reaction time and compared with a similar mean obtained for the light or acoustic stimulus in the absence of road noise This mean was derived from 25 values obtained before the exposure to road noise at its true intensity and 25 after exposure with an attenuation of 20 dB Both of these series were obtained with 25 light or sound signals supplied at randomised intervals over a period of 90

This method of determining reaction times did not neglect the part that tiredness or habituation might play even in the case of randomised signals towards the end of each experiment.

S D s (2 σ) in the absence of traffic noise were calculated for each subject to provide a normal range of reaction times for the significant signal The difference between these values and those observed during exposure to road noise could thus be attributed to interference on the part of such noise with the mechanism required for performance of the simple and complicated reactions.

Overall evaluation of the results was made in the light of the arithmetic means of the data obtained from the 10 subjects in each experimental situation

RESULTS

Table 1 and figs 1 3 and Table 2 and figs. 4-6 show the results for the simple and complicated reaction respectively Reaction times varied from one subject to another and their single and total absolute values were of little significance Meaningful comparisons were thus made by using percent variations.

In the absence of road noise, all 10 subjects reacted much more quickly to the acoustic signal mean times of 24 csec and 34 csec for the simple and complicated reaction respectively as opposed to 29 csec and about 42 csec (reductions of about 18 % and 24 %) when the light stimulus was used

Exposure to real and attenuated road noise made no significant difference to the mean reaction time for the simple reaction following the light signal. Values lay within the spectrum of variation observed in the absence of such noise

When the acoustic signal was given however exposure to real road noise led to an increase of about 24 Attenuation cut back this increase to about 18 % 12 %, 9 and 3 for 5 10 15 and 20 dB reductions in intensity respectively

The picture was the same for the complicated reaction Real and attenuated road noise made no real difference when the light signal was used With the acoustic signal real noise

Table 1. *Simple motor reaction times with and without exposure to road noise. Mean values for 10 subjects following 50 light and 50 sound stimuli*

LIGHT STIMULATION

Experimental conditions	Reaction time in csecs.	Departure from base value	
		absolute	percent
Without exposure to traffic noise (base value)	29.39 (± 3.24 = ± 11.03%)	—	—
Exposure to traffic noise at real intensity	29.03 ± 5.60	− 0.36 ± 1.46	− 1.22 ± 4.96
Attenuation of 5 dB	29.20 ± 5.68	− 0.19 ± 1.78	− 0.64 ± 6.05
Attenuation of 10 dB	29.59 ± 5.78	+ 0.20 + 2.40	+ 0.68 ± 8.16
Attenuation of 15 dB	29.38 ± 5.37	− 0.01 ± 1.44	− 0.03 ± 4.89
Attenuation of 20 dB	29.36 ± 5.57	− 0.03 ± 1.14	− 0.10 ± 3.87

ACOUSTIC STIMULATION

Experimental conditions	Reaction time in csecs	Departure from base value	
		absolute	percent
Without exposure to traffic noise (base value)	24.10 (± 2.63 = ± 10.91%)	—	—
Exposure to traffic noise at real intensity	29.9? ± 7.72	+ 5.82 ± 5.04	+ 24.14 ± 20.91
Attenuation of 5 dB	28.58 ± 6.19	+ 4.48 ± 5.08	+ 18.58 ± 21.07
Attenuation of 10 dB	26.94 ± 5.24	+ 2.84 + 2.46	+ 11.78 ± 10.20
Attenuation of 15 dB	26.28 ± 4.99	+ 2.18 ± 2.62	+ 9.04 ± 10.87
Attenuation of 20 dB	24.77 ± 4.32	+ 0.67 ± 1.28	+ 2.78 ± 5.31

Table 2. *Complicated motor reaction times with and without exposure to road noise. Mean values for 10 subjects following 50 light and 50 sound stimuli*

LIGHT STIMULATION

Experimental conditions	Reaction time in csecs.	Departure from base value	
		absolute	percent
Without exposure to traffic noise (base value)	42.22 (± 3.64 = ± 8.62 %)	—	—
Exposure to traffic noise at real intensity	42.81 ± 6.47	+ 0.59 ± 2.22	+ 1.39 ± 5.25
Attenuation of 5 dB	42.23 ± 6.59	+ 0.01 ± 2.34	+ 0.02 ± 5.54
Attenuation of 10 dB	42.01 ± 6.44	− 0.21 ± 2.36	− 0.49 ± 5.58
Attenuation of 15 dB	42.00 ± 6.61	− 0.22 ± 1.00	− 0.52 ± 2.36
Attenuation of 20 dB	42.13 + 6.59	− 0.09 ± 1.22	0.21 ± 2.88

ACOUSTIC STIMULATION

Experimental conditions	Reaction time in csecs.	Departure from base value	
		absolute	percent
Without exposure to traffic noise (base value)	34.29 (± 3.45 = ± 10.06 %)	—	—
Exposure to traffic noise at real intensity	42.0? ± 8.08	+ 7.73 ± 5.68	+ 22.54 ± 16.56
Attenuation of 5 dB	39.93 ± 7.52	+ 5.64 ± 4.24	+ 16.44 ± 12.36
Attenuation of 10 dB	38.50 ± 6.18	+ 4.21 ± 3.90	+ 12.27 ± 11.37
Attenuation of 15 dB	37.61 ± 6.18	+ 3.32 ± 3.64	+ 9.68 ± 10.61
Attenuation of 20 dB	35.66 ± 6.57	+ 1.37 ± 3.00	+ 3.99 ± 8.74

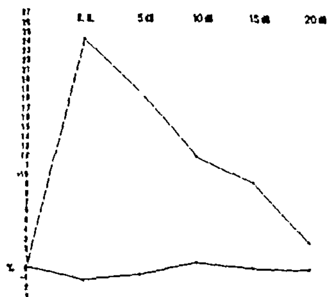


Fig 1 Mean simple motor reaction times following 50 light and 50 sound stimuli in 10 subjects during exposure to traffic noise, expressed as percent variations of similar values (= 0) obtained in the absence of road noise (——•—— light stimulation ---•--- acoustic stimulation)



Fig 4 Mean complicated motor reaction times following 50 light and 50 sound stimuli in 10 subjects during exposure to traffic noise, expressed as percent variations of similar values (= 0) obtained in the absence of road noise (——•—— light stimulation --- --- acoustic stimulation).

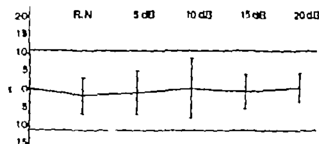


Fig Simple motor reaction to light stimulus. Mean percent variation and S.D of reaction time in 10 subjects on exposure to road noise The dark band indicates the normal range of variation in the absence of traffic noise (same subjects).

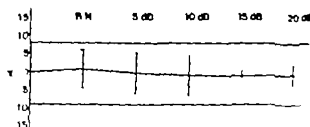


Fig 5 Complicated motor reaction to light stimulus. Mean percent variation and S.D of reaction time in 10 subjects on exposure to road noise. The dark band indicates the normal range of variation in the absence of traffic noise (same subjects).

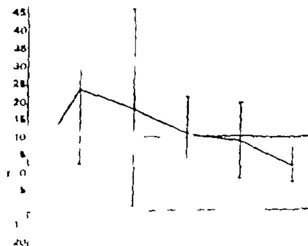
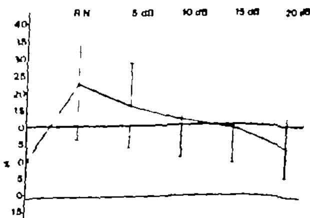


Fig 3 Simple motor reaction to sound stimulus. Mean percent ariation and S.D of reaction t me in 10 subjects on exposure to road noise. The dark band indicates the normal range of variation in the absence of traffic noise (same subjects).



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led to an increase of about 22%, and this was reduced to about 16%, 12%, 10% and 4% with increasing attenuation.

CONCLUSIONS

The first point to emerge from our results is less time is required for the execution of either a simple or a complicated motor reaction in response to an acoustic as opposed to a light signal. No physical or anatomical explanation can be advanced for the constant observation of this difference in all 10 subjects. It is probably the outcome of a difference in attention referable to the spatial features associated with the information that the two stimuli provide.

It is, in fact, obvious that the light stimulus reaches the receptor solely from a well defined visual field that is both in front of us and known to us, whereas a sound can reach our ears from any point of space, even from behind us. This lack of precise definition of the acoustic source probably serves to accentuate our attention prior to the emission of a known and awaited stimulus. This, *in turn*, has a considerable effect on the time required for the ensuing simple or complicated *response reaction*.

Road noise did not alter the mean reaction time in the case of light *stimuli*. *Here* the meaningful light signal and the competing traffic noise were gathered by different receptors and reached the centres via separate and distinct nervous pathways, so that the anatomical substrate for interference was not present.

When, on the other hand, the two signals were gathered by the same receptor and reached the centres via the same pathway a situation arose in which the mean simple and complicated motor reaction times increased by comparison with those for the response to the meaningful signal alone.

When real road noise was used, this increase was as much as 20%. The standard deviation reflects the discontinuity of traffic noise and the different ways in which interference between a meaningful and a competing signal may take place.

Attenuation through the 5 to 20 dB range resulted in gradual decreases in this percentage that were almost the same for the simple and the complicated reaction, though it was not suppressed completely.

These findings are the expression of interference between two signals, apparently in proportion to the intensity of the competing signal. This interference, in its turn, is an expression of the difficulties encountered by the meaningful signal in reaching the centres owing to "partial congestion of the line". It is not eliminated entirely even when the competing signal is attenuated by as much as 20 dB, though it may be supposed that further attenutation would have this effect. This possibility however was not investigated, because it would have involved too distant a departure from real conditions.

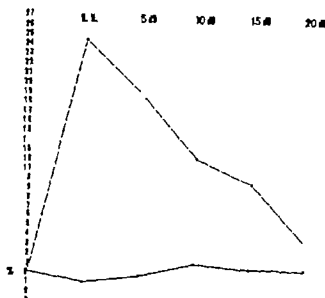


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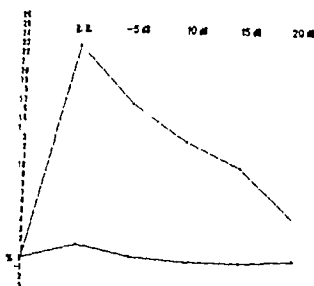


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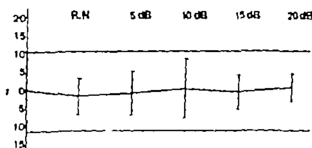


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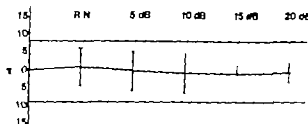


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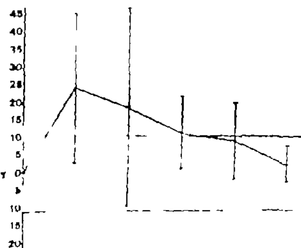


Fig 3 Simple motor reaction to sound stimulus. Mean percent variation and S D of reaction time in 10 subjects on exposure to road noise. The dark band indicates the normal range of variation in the absence of traffic noise (same subjects).

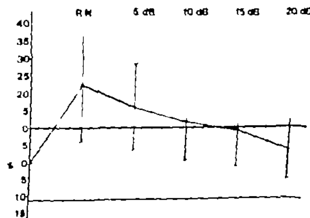


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When real road noise was used, this increase was as much as 20 %. The standard deviation reflects the discontinuity of traffic noise and the different ways in which interference between a meaningful and a competing signal may take place

Attenuation through the 5 to 20 dB range resulted in gradual decreases in this percentage that were almost the same for the simple and the complicated reaction, though it was not suppressed completely

These findings are the expression of interference between two signals, *apparently in proportion to the intensity of the competing signal.* This *interference in its turn, is an expression* of the difficulties encountered by the meaningful *signal in reaching the centres owing to* " partial congestion of the line It is not eliminated *entirely even when the competing signal* is attenuated by as much as 20 dB, though it may be *supposed that further attenuation would* have this effect. This possibility however was *not investigated,* because it would have involved too distant a departure from real conditions.

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CHANGES IN CORTICAL RESPONSIVITY TO MULTISENSORIAL STIMULI DURING EXPOSURE TO URBAN TRAFFIC NOISE

B Bergamasco M Gilli G Rossi

From the Department of Audiology and the Nervous and Mental Diseases Clinic University of Turin Turin, Italy

SCOPE OF THE RESEARCH

As everyone knows, noise disturbs psychic activity On the other hand no attempt has yet been made to determine the neurophysiological mechanisms whereby noise produces its supposed pathogenic action in man. The scanty data in the literature are almost solely confined to the effect noise has on sleep (Rechtschaffen et al 1966 Alexander 1972 a b).

This paper deals with preliminary data collected in an examination of the effect of traffic noise on cortical responsivity to acoustic and visual stimuli

MATERIAL AND METHODS

EEG potentials elicited by acoustic stimuli were measured during several sessions on 20 normal subjects aged 18-35 yr using needle electrodes with unipolar leads in the scalp and a reference electrode on the mastoid during repose and during 10 exposure to road noise (RN). Stimuli and processing of the responses were carried out with a Medelec Amplaid ERA EcoG complex, consisting of an acoustic stimulus generator a 4-track averager and an acoustic generator console for the elaboration of tones and noise. Two loudspeakers 50 cm from the left and right of the subject s head were used to furnish the acoustic signals in a soundproof recording room The acoustic signal was an 80 dB SPL click while an 0 3 J flash was generated by a stroboscope triggered by the computer

A tape consisting of ten 1 minute recordings of daytime RN each taken at different points

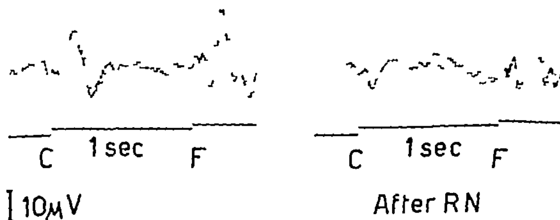


Fig 1 EAP (C) and EVP (F) (mean of 50 values) in the same subject during repose (left) and a few seconds before the termination of a 10' RN tape (right). C indicates the click and F the flash. Note the large change in EAP and steady EVP

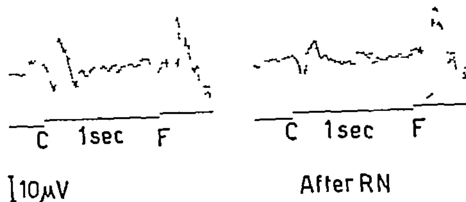


Fig. 2A

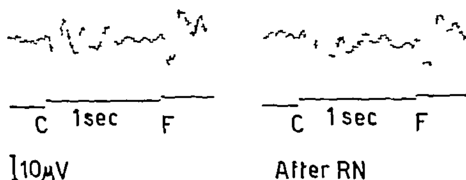


Fig. 2B

Fig. A) EAP (C) and EVP (F) in the same subject during repose (left) and shortly before the termination (right) of 10 RN tape. Each value is the mean of 50 responses. Note the fall in EAP amplitude and scant change in EVP. B) A last, in different subject.

of Turin, was used. Its characteristics were

L_{m} dB	L_{eq} dB	σ ± dB
88.8	89.4	2.35
L_{m} dB(A)	L_{eq} dB(A)	σ ∓ dB(A)
71.6	73.1	3.54

This noise was used at its real intensity which was assessed by a Brüel & Kjaer 2209 phonometer fitted with a model 1613 octave filter placed at the point occupied by the subject's head.

RN was fed through a Uher 4400 stereo I C recorder and then into the recording room via the complex console as already described. Following recordings during repose, acoustic and visual responses were taken during and shortly before stopping the tape. Each stimulus pair consisted of a click followed after 1 by the flash and was fed to the subject at randomised intervals. An average value from 50 responses was used. The p_2-n_2 wave (positive and negative deflections with 80-120 msec latency) was employed in assessment of the elicited acoustic potential (EAP) peak-to-peak amplitude, since these deflections were absolutely constant in all subjects and are free of any myogenic com-

ponent (Cordove et al 1969 Picton et al 1974) The V wave amplitude according to Gastaut (Bergamini and Bergamasco 1967) was used for the elicited visual potential (EVP)

RESULTS

A marked reduction in EAP amplitude was noted in all subjects a few seconds before the tape finished (figs. 1 and 2) whereas no signi ficant change in EVP appeared

The mean EAP for the series was 22.5 μV during repose and 13 75 μV a few seconds before the tape finished i e a difference of 40 6 / (Table 1) These data were statistically significant.

Table 1 *Mean μV value of EAP wave (p_2n_2) during repose and at conclusion of RN for 10' and percent reduction Ranges in brackets*

During repose	22.5	(R 16.1 28 3)
At conclusion of RN for 10	13 75	(R 10.2 20.3)
Percent reduction	40.6	(R 32.2 60 1)

No particular difference in EVP amplitude was observed under these conditions (26 8 μV during repose 25 75 μV after RN) Some subjects *indeed displayed an increase in amplitude* after exposure to RN

CONCLUSIONS

A dramatic fall in EAP and no change in EVP are the consequences of 10 exposure to RN This difference is open to three possible explanations

1) activation by RN of the ascending reticular system and reduction in cortical response amplitude and EEG desynchronization due to occlusive convergence in accordance with the data of Bremer (1958) and Naquet et al (1960)
2) cochlear inhibition on the part of centrifugal acoustic pathways in accordance with the experimental data collected by Galambos (1956)
3) cortical inhibition

Possibility 1) is ruled out by the absence of any fall in EVP after RN Moreover EEG desynchronization disappears a few minutes later The second possibility is at present devoid of supporting evidence while further data are necessary before accepting the possibility of cortical inhibition Some of these (behaviour of the contingent negative variation during RN) are been investigated (see next paper)

All that can be said so far is that changes in cortical responsitivity to multisensorial stimuli after exposure to RN concern the acoustic stimulus only i e. sensoriality related to RN itself

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Acta Otolaryng Suppl 339 27 29 1976

BEHAVIOUR OF CNV DURING EXPOSURE TO URBAN TRAFFIC NOISE

B. Bergamasco, P Benna, A. M Covacich, M Gilli, G Rossi

From the Department of Audiology and the Nervous and Mental Diseases Clinic University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

In previous research, we observed that during administration of road noise modifications take place in cortical response that exclusively involve evoked acoustic potential, whereas responses evoked by other sensorial modalities show no variation. The clear-cut reduction in evoked response may be interpreted as the consequence of noise-induced neuronal occlusion (noise occupies neurones at the expense of the acoustic stimulus and not of other stimuli evoking cortical potential). Our experimental findings confirm the masking effect of noise on verbo-acoustic communications and it is notorious that noise disturbs these as early as 40 dB and makes them impossible beyond 80-90 dB

The present paper examines the problem of whether road noise modifies cortical responsiveness t psychological as well as to sensorial stimuli The Contingent Negative Variation has been used as a parameter for this reason.

MATERIAL AND METHODS

The research was carried out on 1 volunteers of both sexes and aged between 21 and 33 yrs. Their hearing was normal. The Contingent Negat e Variation (CNV) was recorded in conditions of normal quiet background and during administration of road noise (RN).

The road noise employed consisted of 10 recordings of 1 each made at 10 different points in Turin during the hours of daytime traffic The following road noise data, in terms of L_m and L_{eq} were adopted

L_m dB	L_{eq} dB	$\sigma +$ dB
88.8	89 4	2.35
L_m dB(A)	L_{eq} dB(A)	$\sigma +$ dB(A)
71 6	73 1	3.54

The road noise was used with real intensity characteristics valued by means of a Brüel and Kjaer mod. 2209 phonometer with mod 1613 octave filter at the subject s head.

The tape was played on a Uher 4400, Report Stereo 1 C, recorder and the road noise was then put through an Elit 815 audiometer into a free field from two speakers half a *meter* apart on the right and left of the subject.

CNV was recorded in traditional fashion The subject was laid on a bed in a twilit room with a sound-proofed flasher 40 cm from his eyes (flash 0.3 J) while a pair of loud-speakers 10 cm right and left of his head and connected to an acoustic generator supplied an 80 dB SPL click. The flasher and acoustic generator were connected with the central stimulus programmer Monopolar frontal EEG recording was carried out by means of needle-electrodes and the cerebral bioelectric lead was connected to an O T.E. 1172 Neuroaverager *This* provides correlated averages it possesses an analogic-digital interface that makes it possible to choose between automatic and manual operation. Manually each sweep containing the CNV can be viewed for 3 those spoiled by

ponent (Cordove et al 1969 Picton et al 1974) The V wave amplitude according to Gastaut (Bergamini and Bergamasco 1967) was used for the elicited visual potential (EVP)

RESULTS

A marked reduction in EAP amplitude was noted in all subjects a few seconds before the tape finished (figs. 1 and 2) whereas no significant change in EVP appeared

The mean EAP for the series was 22.5 μV during repose and 13 75 μV a few seconds before the tape finished i e a difference of 40 6 % (Table 1) These data were statistically significant.

Table 1 *Mean μV value of EAP wave (p_2-n_2) during repose and at conclusion of RN for 10 and percent reduction Ranges in brackets*

During repose	22.5	(R 16.1 28.3)
At conclusion of RN for 10	13 75	(R 10.2 20.3)
Percent reduction	40.6	(R 32.2 60 1)

No particular difference in EVP amplitude was observed under these conditions (26 8 μV during repose 25 75 μV after RN) Some subjects indeed displayed an increase in amplitude after exposure to RN

CONCLUSIONS

A dramatic fall in EAP and no change in EVP are the consequences of 10 exposure to RN This difference is open to three possible explanations

1) activation by RN of the ascending reticular system and reduction in cortical response amplitude and EEG desynchronization due to occlusive convergence, in accordance with the data of Bremer (1958) and Naquet et al (1960)

2) cochlear inhibition on the part of centrifugal acoustic pathways, in accordance with the *experimental data collected by Galambos* (1956)

3) cortical inhibition

Possibility 1) is ruled out by the absence of any fall in EVP after RN Moreover EEG desynchronization disappears a few minutes later The second possibility is at present devoid of supporting evidence while further data are necessary before accepting the possibility of cortical inhibition Some of these (behaviour of the contingent negative variation during RN) are been investigated (see next paper)

All that can be said so far is that changes in cortical responsivity to multisensorial stimuli after exposure to RN concern the acoustic stimulus only i e sensoriality related to RN itself

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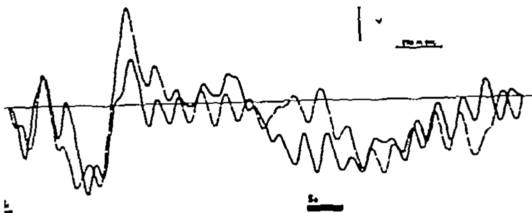


Fig. 2. CNV (averaging of 25 responses) obtained in the same subject during normal quiet background (continuous line) and during RN administration (interrupted line). Note the greater amplitude of the CNV recorded during RN.

variations were not uniform. One group (A, Table 1) presented a fall in CNV amplitude during RN (fig. 1), another group (B Table 1) an increase (fig. 2), while in two cases (C, Table 1), no modifications were observed at all.

It goes without saying that statistical analysis of the variation in CNV amplitudes of the group as a whole did not show any significance ($P < 0.30$). Nor was the CNV amplitude fall observed in four subjects (group A, Table 1) during administration of a quiet background statistically significant ($P < 0.10$). Only in group B of Table 1 (a group in which CNV presented increased amplitude during RN administration) was there any statistical significance ($P < 0.01$).

CONCLUSIONS

The findings show clearly that RN acts differently on the psychoattentive functions of the various subjects.

Moreover it is well known that the subjective sensation of "unpleasantness irritation" induced by noise does not arise at any specific intensity level but within ranges depending on the subject (between 40 and 90 dB according to Kryter 1970). The intragroup variability of CNV amplitude as observed by us confirms the above. But it is even more interesting to note that in a certain number of subjects CNV amplitude falls and in others it increases, as if to suggest that in the former RN irritates the psychoattentive processes set in motion by CNV while in the latter it facilitates them. Clearly the reason for this difference must be sought in the way in which noise triggers basic psychological mechanisms, in other words, in the way the subject lives noise. The modality we have observed most frequently (and the only *one* confirmed statistically) has been that whereby noise facilitates the slow depolarization of the cortex and CNV consequently increases in amplitude. Perhaps in this case the subject troubled by noise enhances his mental concentration while in the other group noise distracts the subject and so brings on a reduction in expectation and a consequently low amplitude CNV.

As we have already mentioned, this hypothesis fits in with the extreme diversity from one subject to another in the way in which noise is lived as an annoyance or at times, as a pleasure (just think of habitués of pop music shows!).

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eye or blinking movements thus being rejected The flash and click stimuli were distributed by a random stimuli programmer in the following sequence (trial) one flash (S_1) followed at 1100 msec by a series of clicks (S_2) at 10 c/sec, lasting 500 msec A random time of between 4 and 10 sec separated each trial A set of trials (flash + clicks) was first administered to eliminate the orientation reflex and create a condition of habituation to the stimuli the subject was then ordered to use the switch by his right hand in order to interrupt the series of clicks following the flash The CNV was obtained by summing 25 trial presentations and was recorded on paper by an X Y Moseley Plotter

RESULTS

*The CNV's recorded in 12 subjects in condi*tions of normal quiet background and during RN were considered The morphology duration and amplitude of each CNV were assessed No CNV duration modifications were observed in the two different experimental situations, only morphology modifications arising out of variations in amplitude which was measured at the point of maximum negative deflexion with respect to the baseline (Table 1)

In our research amplitude data are lower than those given in the literature because our computer unlike others utilized up to the pre-

Table 1 *Amplitude in μV of the CNV recorded during a normal quiet background and during the administration of road noise (RN) Statistical significance data are shown for groups A and B The difference between the CNV amplitudes in the three groups considered overall was not statistically significant ($P < 0.30$)*

Subject	CNV amplitude (μV) during normal quiet background	CNV amplitude (μV) during RN
M F 28 y	2.75	1 65
C.C. 23 y	6.6	2.86
L.G 33 y	12.37	11
A C. 24 y	7 15	6.6
GROUP A P < 0 10		
F M 23 y	4 18	8.25
B P 24 y	12.76	15 6..
B L. 23 y	4 95	9 9
M L. 31 y	2.86	6.6
C.A 27 y	11.27	12.37
D L. 4 y	11	13
GROUP B P < 0 01		
G M 23 y	8 8	8 8
G Ma 21 y	7 7	7 7
GROUP C		

sent provides arithmetic means of each phenomenon and not sums of means. Although no modification was ever observed in the duration and form of the CNV's recorded with a normal quiet background and during RN amplitude

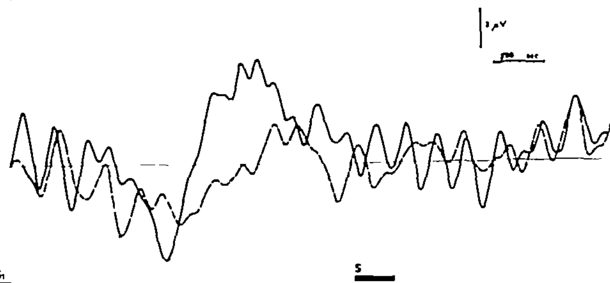


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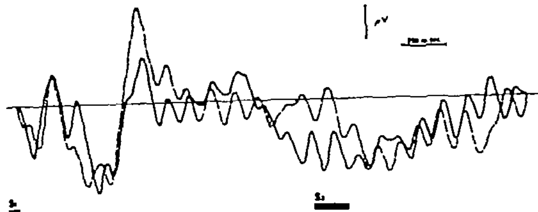


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In our research amplitude data are lower than those given in the literature because our computer unlike others utilized up to the present, provides arithmetic means of each phenomenon and not sums of means. Although no modification was ever observed in the duration and form of the CNV's recorded with a normal quiet background and during RN amplitude

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B.P	24 y	12.76	15 62
B.L.	23 y	4 95	9 9
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C.A.	77 y	11._7	12.37
D L.	24 y	11	13.2
GROUP B P < 0 01			
G M	23 y	8 8	8.8
G.Ma.	21 y	7 7	7 7
GROUP C			

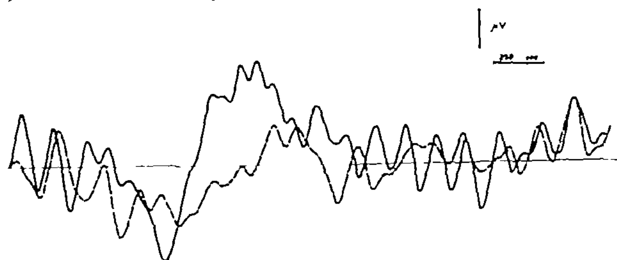


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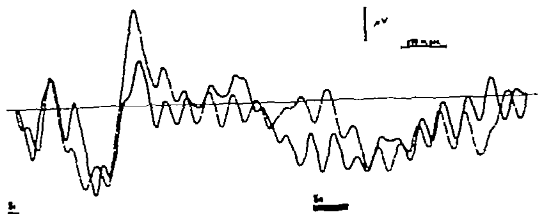


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EEG CHANGES INDUCED BY EXPOSURE TO URBAN TRAFFIC NOISE AND WHITE NOISE

B Bergamasco P Benna, A M Covacich M Gilli

From the Department of Audiology and the Nervous and Mental Diseases Clinic University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

Previous personal work had disclosed a marked reduction of acoustic response but unchanged visual response on the part of the cortex fol lowing exposure to traffic noise An interpre tation for this pattern of cortical responsivity was sought by examining the EEG changes induced by the administration of road noise (RN) and white noise (WN) respectively

MATERIAL AND METHODS

A tape consisting of ten 1 minute recordings of daytime RN each taken at different points of Turin was used Its characteristics were

L_m dB	L_{eq} dB	σ + dB
88 8	89 4	2 35
L_m dB(A)	L_{eq} dB(A)	σ + dB(A)
71 6	73 1	3 54

This noise was fed through a Uher 4400 stereo I C recorder into the circuit of an Elit 815 audiometer and then passed to the subject via two loudspeakers placed 50 cm to the left and right of his head An evaluation of RN atte nuated by 20 dB SPL was made at the point occupied by the head using a Brüel & Kjaer phonometer 2209 with a model 1613 octave filter WN was supplied at 85 dB SPL by the same audiometer

RESULTS

The most interesting finding (Table I) was the virtual absence of EEG desynchronization pro- duced by both RN and WN in 9 subjects of the group of 10 subjects considered Desyn chronization was indeed noted but for brief repeated periods (max 6-10") throughout ex posure Surprisingly at the start of exposure it was very brief (2 3") and there was no " orien- tation reaction " It was also seen that desyn chronization caused by WN was always much less, in spite of its greater intensity One subject, however displayed marked and lasting desyn- chronization on exposure to each type of noise This fact, coupled with the observation that desynchronization due to mental calculation in silence and on exposure to RN ad WN differed in all 10 subjects suggested that a Rorschach test should be run to see whether personality differences were affecting the EEG response to noise

A relation was found between basic affective components of personality and noise-induced EEG desynchronization as well as that induced by mental calculation in silence and on exposure to noise (fig 1 and 2).

CONCLUSIONS

The following conclusions can be drawn with respect to the effect of noise on the CNS noise leads to a reduction in cortical responsivity with respect to sensoriality related to sound itself and not to other sensorial stimuli in other words reduction of the potential elicited as the acoustic response and no effect on the visual response (see previous paper but one) RN and

Table 1 *EEG desynchronization time percents during road noise (RN) and white noise (WN) during repose, arousal reaction, and mental calculation*

Subjects	Time of R.N calculation	Time of W.N calculation	% of desynchronization time induced by R.N	% of desynchronization time induced by W.N	% of desynchronization time induced by arousal reaction without R.N	% of desynchronization time induced by chaps without R.N	% of desynchronization time induced by mental calculation during W.N	% of desynchronization time induced by mental calculation without R.N	% of desynchronization time induced by mental calculation during R.N
C.A. 27 y	21' 30"	10'	17 %	11	100 %	100 %	53.5 %	38.4 %	75 %
F.M. 28 y	19'	10'	19.6 %	5.4 %	100 %	100 %	55 %	90	33
G.C. 25 y	23' 30"	10'	85 %	75.8 %	100 %	100 %	100 %	100 %	100 %
G.M. 21 y	15'	10'	29.85 %	6.8 %	100 %	100 %	45	59.6 %	50 %
D.L. 24 y	22' 30"	10'	16.3 %	14.6 %	100 %	100 %	50 %	57	50 %
B.P. 24 y	27' 30"	10'	14.8 %	6.9 %	100 %	100 %	80 %	75	65 %
C.C. 19 y	31'		18.7 %		100 %	100 %	58 %	52.7 %	
A.C. 24 y	17' 20"	10'	17 %	5.6 %	100 %	100 %	22.7 %	23	20
L.G. 33 y	27'		8.3 %		100 %	100 %	46.8 %		
G.A. 32 y	4'		12 %		100 %	100 %	100 %		

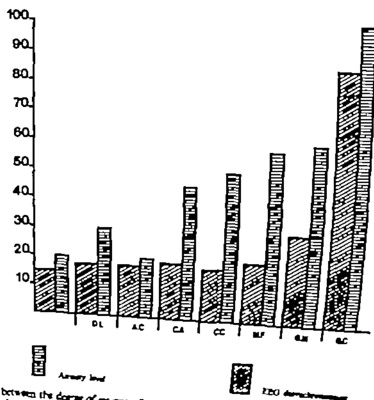


Fig. 1. Relation between the degree of [illegible] of affection (IDA) as shown by the Rorschach test, and percent of desynchronization induced by RN. The correlation between these parameters is particularly marked at subjects B. P., D. L. and A. C. (reduced IDA and the lowest desynchronization) and in subject G. C. (very high IDA and highest desynchronization). [illegible]

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EEG CHANGES INDUCED BY EXPOSURE TO URBAN TRAFFIC NOISE AND WHITE NOISE

B Bergamasco P Benna, A M Covacich M Gilli

From the Department of Audiology and the Nervous and Mental Diseases Clinic University of Turin, Turin Italy

SCOPE OF THE RESEARCH

Previous personal work had disclosed a marked reduction of acoustic response, but unchanged visual response on the part of the cortex following exposure to traffic noise An interpretation for this pattern of cortical responsivity was sought by examining the EEG changes induced by the administration of road noise (RN) and white noise (WN) respectively

MATERIAL AND METHODS

A tape consisting of ten 1 minute recordings of daytime RN each taken at different points of Turin was used Its characteristics were

L_m dB	L_{eq} dB	σ + dB
88 8	89 4	2.35
L_m dB(A)	L_{eq} dB(A)	σ + dB(A)
71 6	73 1	3 54

This noise was fed through a Uher 4400 stereo I C recorder into the circuit of an Elit 815 audiometer and then passed to the subject via two loudspeakers placed 50 cm to the left and right of his head An evaluation of RN attenuated by 20 dB SPL was made at the point occupied by the head using a Brüel & Kjaer phonometer 2209 with a model 1613 octave filter WN was supplied at 85 dB SPL by the same audiometer

RESULTS

The most interesting finding (Table 1) was the virtual absence of EEG desynchronization produced by both RN and WN in 9 subjects of the group of 10 subjects considered Desynchronization was, indeed noted but for brief repeated periods (max 6-10") throughout exposure Surprisingly at the start of exposure it was very brief (2 3") and there was no " orientation reaction It was also seen that desynchronization caused by WN was always much less, in spite of its greater intensity One subject, however displayed marked and lasting desynchronization on exposure to each type of noise This fact, coupled with the observation that desynchronization due to mental calculation in silence and on exposure to RN ad WN differed in all 10 subjects suggested that a Rorschach test should be run to see whether personality differences were affecting the EEG response to noise

A relation was found between basic affective components of personality and noise-induced EEG desynchronization, as well as that induced by mental calculation in silence and on exposure to noise (fig 1 and 2)

CONCLUSIONS

The following conclusions can be drawn with respect to the effect of noise on the CNS noise leads to a reduction in cortical responsivity with respect to sensoriality related to sound itself and not to other sensorial stimuli in other words reduction of the potential elicited as the acoustic response and no effect on the visual response (see previous paper but one) RN and

Table 1 *EEG desynchronization time percents during road noise (RN) and white noise (WN) during repose arousal reaction, and mental calculation*

Subjects	Time of R N administration	Time of W N administration	% of desynchronization time induced by R.N	% of desynchronization time induced by W N	% of desynchronization time induced by arousal reaction without R.N.	% of desynchronization time induced by clap without R.N.	% of desynchronization time induced by mental calculation during W N	% of desynchronization time induced by mental calculation without R.N.	% of desynchronization time induced by mental calculation during R.N
C A. 27 y	21' 30"	10'	17 %	11 %	100 %	100 %	53.5 %	38.4 %	75 %
F M 28 y	19'	10'	19 6 %	5 4 %	100 %	100 %	55 %	50 %	33 %
G C 25 y	23' 30"	10'	85 %	73.8 %	100 %	100 %	100 %	100 %	100
G.M. 21 y	15'	10'	29 85 %	6 8 %	100 %	100 %	45 %	59.6 %	50 %
D L. 24 y	22' 30"	10'	16.3 %	14 6 %	100 %	100 %	50 %	57 %	50 %
B P 24 y	27' 30"	10'	14 8 %	6.9 %	100 %	100 %	80 %	75 %	65 %
C C 19 y	31		18 7 %		100 %	100 %	58 %	52.7 %	
A C. 24 y	17' 20"	10'	17 %	5 6 %	100 %	100 %	22.7 %	23	20 %
L G. 33 y	27		8.3 %		100 %	100	46.8 %		
G A. 32 y	24		12 %		100 %	100 %	100 %		

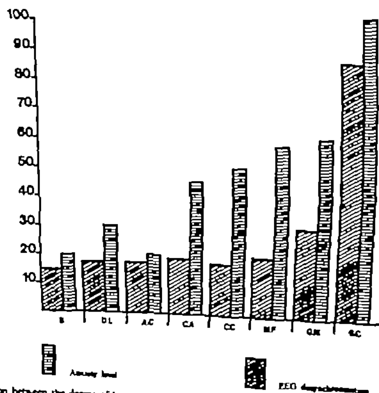


Fig 1 Relation between the degree of intimate dissonance of affection (IDA), as show by the Rorschach test, and percent of desynchronization induced by RN. The association between these parameters is particularly marked in subjects B P D L and A C (reduced IDA and the lowest desynchronization %) and in subject G C (very high IDA and highest desynchronization %). The remaining cases display similar proportionality

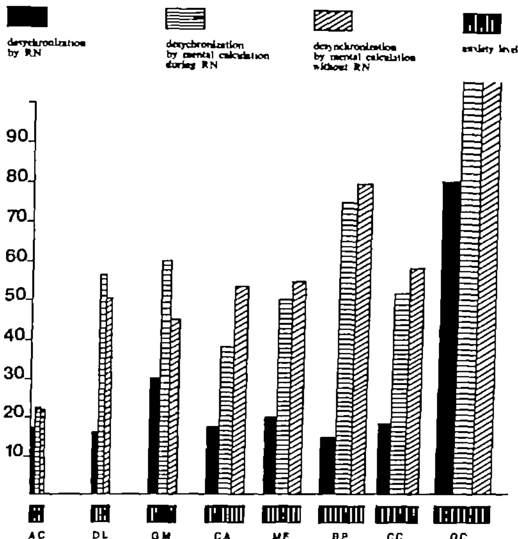


Fig. 2 Relation between EEG desynchronization induced by RN and by mental calculation (with and without RN) and individual mental anxiety (Rorschach test). Anxiety is highest in cases where desynchronization caused by mental calculation during RN is less than during response. This suggests that RN acts as a " tranquilliser " of anxiety in subjects whith a high anxiety level, with the result that the calculation itself causes less desynchronization

WN result in no more than slight EEG desyn chronization (and hence activation of the diffuse projection system) No " orientation reaction " is noted and there is no habituation A clear relation can also be discerned between the subject's overall affective component and his degree of desynchronization in response to noise and mental calculation Noise, in fact, can endured in a variety of ways. On the other hand these relations are not apparent in the changes of cortical responsivity to sensorial stimuli.

As matters now stand no satisfactory neurophysiological interpretation can be offered for these findings.

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HUMAN SLEEP MODIFICATIONS INDUCED BY URBAN TRAFFIC NOISE

B Bergamasco, P Benna, M Gilli

From the Department of Audiology and the Nervous and Mental Diseases Clinic University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

In previous research, we examined the effects of noise on various cerebral electrophysiological parameters with the encephalon in waking state. As it is widely believed that noise is the major sleep-disturbance factor we undertook a study of the modifications induced by road noise on human EEG during sleep road noise being an element of stress which is becoming more and more important, especially in large towns.

The literature, however contains few reports by workers who have studied the way in which noise interferes in this highly important factor in human homoeostasis. On the one hand, Kryter (1970) has highlighted the importance of certain noise characteristics (its intensity its unexpectedness, or the fact that it belongs to the subject s normal habitat, its continuity in time or the intermittence of its source) on the other Alexandre (1972 a, b) has demonstrated the importance of inherent factors within each individual These vary with the stage of sleep and the subject s age, sex, character and state of health. It is equally true, however that to some extent the subject manages to adapt to greater or less noise in his environment Schieber et al (1968) have shown that the depth of sleep falls proportionally to the background noise against which the subject sleeps. It has also been noted that the more an organism is in need of sleep, the higher becomes its threshold to noise stimuli This, however does not belie the current belief that noise disturbs a person tryi g to sleep

MATERIAL AND METHODS

Our research into the effects of road noise on sleep was carried out with the assistance of five normal volunteers of both sexes and aged between 23 and 32.

The road noise employed consisted of 3 recordings of night-time traffic made in 3 different points of Turin lasting 15 min each with intervals of 15 min silence. These were put on to 4 tapes of 90 min each to enable us to carry out experiments lasting 6 hours.

The road noise data in terms of L_{m} and L_{eq} were as follows

[illegible]	[illegible]	L [illegible]	L_{eq} [illegible]	[illegible]	L [illegible]	L_{eq} [illegible]	+ [illegible]
1	0-15	63.3	63 6	1 7	53.7	54 7	1.6
2	15-30	87 7	89 3	4 1	74 9	76 9	4 3
3	30-45	63 4	63 8	1.6	54	54	0.6
4	45-60	86.5	88 7	4 62	71.6	74	4.2
5	60-75	63 9	64 2	1.65	54 2	54.2	0 86
6	75-90	87 9	90 7	4.5	75.4	77 7	4.45

The road noise was used with real intensity characteristics valued by means of a Brüel and Kjaer mod. 2209 phonometer with mod. 1613 octave filter at the subject s head

The tape was played on a Uher 4400 Report Stereo I C tape-recorder and put throug an Elit 815 audiometer into a free field from a speaker located half a metre from the subject s head. The subject was laid on a normal bed in a darkened room of the EEG section of the Clinic of Nervous and Mental Diseases, University of Turin.

Table 1 *Percentage values of the duration of the various stages of sleep in 5 normal subjects during administration of road noise compared with the average duration values of sleep phases in the normal adult*

Subjects	Aw	1.st St.	2.nd St	3.rd St	4.th St	REM St.
Sleep mean values in normal adult subjects	1	6	48	7	15	23
G P 23 y	7.8	11 5	35 8	6.5	9.8	29 6
M.A 26 y	2	9.3	59 8	16.9	0.9	11 1
R.G 26 y	10 6	11 6	33 7	10 8	5 7	27.6
C.F 32 y	21.5	14 6	38.8	16.9	8.2	0
C.P 30 y	3.5	12.9	51 6	7.9	6.2	17 9

Each subject began with a night of sleep during which noise was administered in the manner indicated in order to obviate those psychological problems which classically disturb the sleep of the normal adult (change of bed environment, background noise) The following night, EEG ECG and EOG were recorded using needle electrodes to permit subjects some motility during sleep

Before examining the results, it should be borne in mind that we did not compare sleep morphology during noise with the normal sleep morphology of the same subjects but with average statistical data in spite of the fact that each individual has his own sleep modalities.

This is because it was our intention to highlight the acute effects of noise with respect to an ideal functional situation Nor did we investigate the adaptation modalities of the nervous system obliged to sleep in a noisy environment

RESULTS

The results showed quantitative and qualitative alterations to sleep (Table 1)

First of all the arousal phase (including the waking period prior to going off to sleep as well as arousals during the night) was of greater duration percentage wise than normal values, obviously meaning a reduction in total sleep duration in its various stages.

The sleeping phase was much longer in all subjects, as may be seen in the percentage data relating to stage I although this, as already

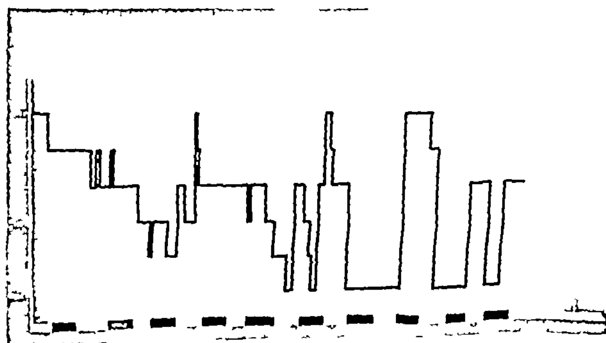


Fig 1 Hypnogram of a normal subject during administration of road noise Not the lengthening of the sleeping stage Hypnogram substantially preserved. (*white* silence *black* noise).

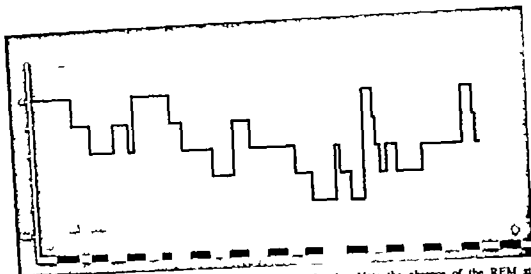


Fig. 2. Hypnogram of subject during administration of road noise. Note the absence of the REM stage. (white = silence black = noise).

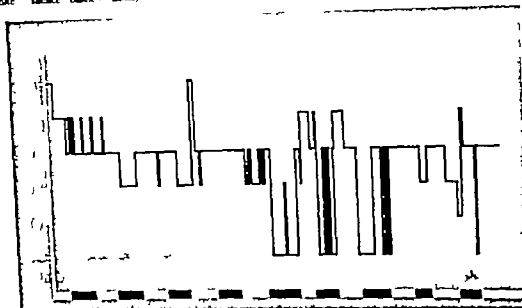


Fig. 3. Hypnogram of subject during administration of road noise. Note frequent periods of light sleep and the short duration of REM and IV stages. (white = silence black = noise)

mentioned, takes in the numerous episodes of light sleep that occurred during the night. The duration of stage II was substantially the same while that of stage III was slightly increased, logically enough (this is the stage during which the "K complexes" occur namely those bioelectric cortical potentials that would appear to be evoked by somatoaesthetic sensations and by external stimuli related to the state of marked neuronal hyperexcitability encountered in this stage of sleep). Alterations observed in stage IV were more marked (this is the stage of deep sleep during which the cortex produces large slow waves and loses its ability to respond to internal and external stimulation) the duration of stage IV was markedly reduced in all cases. The finding is of notable importance because this sleep stage is indispensable for CNS recuperation like REM sleep as is shown by sleep deprivation data (West, 1967).

The length of REM sleep was not substantially changed compared to average values in three of our cases in one case, the percentage of REM sleep was of short duration while another subject had no REM sleep at all. These latter two subjects enjoyed short percentage periods of IV sleep and high percentage periods of arousal (figs. 1 2, 3) It should be pointed out at this point that prior to EEG our subjects were put through personality tests and those presenting the most marked REM stage changes were found by these tests to be of " anxiety introversion " type

Although not disconnected with the subject's basic personality characteristics, these results still point to the gravity of the " noise-sleep disturbance " problem when it is considered that in our experimental situation, the night time noise administered was that of " normal " roads at various points in Turin

CONCLUSIONS

Our conclusions indicate that noise is a disturbing factor for the most delicate and demanding functions of the CNS in a high percentage of subjects and modifies the normal state of vigilance and particularly the regularity of sleep With the present techiques, this may be observed objectively in those " normal " subjects who present some instability in emotion control mechanisms We believe that in subjects where such control is disturbed (neurotics for instance) the effects are much more manifest and harmful and it is also likely that in such subjects noise plays a part in the development of mental disease symptomatology

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EFFECTS OF URBAN TRAFFIC NOISE IN RELATION TO BASIC PERSONALITY

B Bergamasco, P Benna, P Furlan, M Gilli

From the Department of Audiology and the Nervous and Mental Diseases Clinic, University of Turin, Turin, Italy

Previous studies of cortical responsiveness to sensorial stimuli during the administration of Road Noise (RN) has offered uniform, statistically significant data only in the case of certain parameters such as Evoked Acoustic Potential (EAP) and Evoked Visual Potential (EVP). The other neurophysiological data (EEG desynchronization percentage and Contingent Negative Variation CNV) obtained with a normal quiet background and during the administration of RN have not on the whole shown any statistically significant difference. The only possibility for interpreting the data was to establish, by investigating basic personality at what level of mental structure (and possibly in what way) noise acts.

We therefore put 12 subjects through the Rorschach test. Of all the parameters available, we obviously preferred those touching on affectivity namely "deep affective discordance" and "anguish" meaning by the former a central mental process and by the latter a more peripheral process close to the receiving organ (cortical stratum of Freud's ego) of sensory perceptions and mental reaction admission. In this way the mental sphere which is at one and the same time the site of the personality's deepest drives and feelings, may mediate between perception (centripetal) and reaction (centrifugal), although the reactions arising out of this sphere are blinder and less well controlled. By the term "anguish" we mean the strength of the defences, the strength of the ego or "extra tensional anguish" in Rorschach terminology.

We are well aware that it is methodologically wrong to correlate parameters which are on scientifically different levels but a personality structure, or the depth of anguish, cannot yet be quantified electrophysiologically hence our desire to quantify the two basic parameters of the Rorschach test. By using such an approach, we were able to isolate two classes of subjects and obtain statistically significant electrophysiological data.

In a first group (Table 1 Group A) no difference was noted in the amplitude of CNV in relation to normal quiet background and RN while the greater percentage of EEG desynchronization during RN was highly significant. The investigation based on Rorschach's test showed shallow affective discordance and a high level of anguish.

In a second group of cases (Table 1 Group B) a statistically significant increase in CNV amplitude was encountered during noise, while the EEG desynchronization percentage was not statistically different during normal quiet background and RN. In these cases, Rorschach's test highlighted deep affective discordance and a medium-to-low level of anguish. In such subjects, noise takes the place of the intratensional disturbing situation within the perceptive sphere thus facilitating the process of awaiting an event (and hence the CNV) and reducing EEG desynchronization.

Finally in a third group (Table 1 Group C), previous findings were confirmed. There were no substantial differences in CNV amplitude

Table 1 *Effects of urban traffic noise in relation to basic personality*

Group	Subjects	CNV during psychosensory rest. Amplitude in μV	CNV during RN Amplitude in μV	% EEG desynchronization during psychosensory rest	% EEG desynchronization during RN	Rorschach's test. Deep affective dissonance	Rorschach's test. Anguish's level
Group A	M F 28 y	_75	1.65	4.3	4.9	low	high
	G M 21 y	7 7	7 7	1.5	5 1	low	high-elevated
	G M _3 y	8.8	8 8	9.3	17 1	low	high-elevated
	C.C. 23 y	6 6	2.86	7.3	7.3	low	high
	C.A. 27 y	11.27	12.37	8.83	15 69	medium low	very-high
		P < 0.05 S.D ± 1.84		P < 0 001 S.D ± 3.53			
Group B	F M 23 y	4 18	8.25	7.3	5.8	very high	medium-high
	B P 24 y	12.76	15 62	5	2.3	high	low
	B L 23 y	4.95	9.9	22.16	4 83	very high	low
	M L 31 y	_86	6.6	11.3	6.6	high	medium-high
	L.G 33 y	12.37	11	10 5	5 45	medium high	low
		P < 0.001 S D ± 2.47		P < 0.60 S.D ± 6.35			
Group C	D L _4 y	11	13.2	0	1	low	low
	A.C. 24 y	7 15	6.6	_5	1	medium high	medium-high
		P = N.S		P = N.S.			

and the EEG desynchronization percentage in the two experimental situations (normal quiet background and RN) But owing to the particularly complex structures of personalities in this group Rorschach's test did not throw up any unquestionable significance in the two chosen parameters. The results thus confirm the fundamental importance of basic personality in the way noise is lived and its greater or smaller capacity to disturb

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MEASUREMENT OF PHONATORY LEVEL IN THE PRESENCE OF URBAN TRAFFIC NOISE

O Schindler M. Vigone

From the Department of Audiology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

Modifications in the laryngeal or more broadly verbal effector as a response to the presence of a pre-established environmental noise (road noise) have been examined with a view to creating a more favourable signal/noise relation in verboacoustic communication.

MATERIAL AND METHODS

The examination procedure involved having a prose passage read by subjects in a quiet room, the phonatory level was measured by means of a *Brüel & Kjær* mod. 2209 phonometer with mod. 1613 octave filter (scale dB A) placed 5 cm from the mouth (and nose). Sound pressure level was recorded by means of a Brüel & Kjaer mod. 2305 recorder and data were subsequently processed.

The same measurements were then repeated during administration into both earphones of road traffic noise with real intensity characteristics.

The noise recorded on the tape consisted of ten recordings of one minute each carried out at ten different points of Turin during daytime

The following road noise data, in terms of L_m and L_{eq} were adopted

L_m dB	L_{eq} dB	$\sigma +$ dB
88.8	89 4	2.35
L_m dB(A)	L_{eq} dB(A)	$\sigma +$ dB(A)
71.6	73 1	3.54

The tape was played on a Uher 4400 Stereo Report *I C* recorder and transmitted to an Amplaid 500 audiometer calibrated in SPL.

Female subjects aged between 18 and 21 free from organic and functional phonoarticular defects, were chosen.

RESULTS

The experiments were confined to 5 + 5 in view of the homogeneity of the subjects and the small standard deviation (2 σ).

Results are shown in Table 1 fig. 1 shows an example of one of the charts obtained during the experiment.

Table 1 *Equivalent phonatory levels obtained without and with road noise*

Subjects	dB (A) without noise	dB (A) with noise
R P	62.5	68.3
M.G.	64.5	75.5
B D	60 0	71.5
P.P	65 7	74.8
L.O	62.6	73.5
Average value	63 06 ± 2.18	72.72 ± 2.90

Values have been considered as an expression of phonatory level, namely as an expression of the level of laryngeal sound modified by the resonance cavities even though in fact they express the sum of the levels of phonemes produced prevalently at laryngeal level and of

Table 1 *Effects of urban traffic noise in relation to basic personality*

Group	Subjects	CNV during psychosensory rest. Amplitude in μV	CNV during RN Amplitude in μV	EEG desynchronization during psychosensory rest	% EEG desynchronization during RN	Rorschach's test. Deep affective dissonance	Rorschach's test. Anguish's level
Group A	M F 28 y	[illegible]75	1 65	4.3	4 9	low	high
	G M 21 y	7 7	7 7	1.5	5 1	low	high-elevated
	G M 23 y	8.8	8 8	9.3	17 1	low	high-elevated
	C.C. 23 y	6.6	2.86	7.3	7.3	low	high
	C.A 27 y	11 27	12.37	8 83	15 69	medium low	very-high
		P < 0 05		P < 0.001			
		S.D ± 1.84		S.D ± 3.53			
Group B	F M [illegible]3 y	4.18	8.[illegible]5	7.3	5.8	very high	medium-high
	B.P [illegible]4 y	12.76	15 62	5	[illegible]3	high	low
	B.L. [illegible]3 y	4 95	9 9	22.16	4 83	very high	low
	M L. 31 y	2.86	6 6	11.3	6.6	high	medium-high
	L.G 33 y	12.37	11	10.5	5 45	medium high	low
		P < 0 001		P < 0 60			
		S D ± [illegible]47		S.D ± 6.35			
Group C	D L. 4 y	11	13.2	0	1	low	low
	A C. 4 y	7 15	6.6	[illegible]5	1	medium high	medium-high
		P = N.S.		P = N.S.			

and the EEG desynchronization percentage in the two experimental situations (normal quiet background and RN). But owing to the particularly complex structures of personalities in this group, Rorschach's test did not throw up any unquestionable significance in the two chosen parameters. The results thus confirm the fundamental importance of basic personality in the way noise is lived and its greater or smaller capacity to disturb

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INTELLIGIBILITY OF SPOKEN WORDS IN THE PRESENCE OF URBAN TRAFFIC NOISE

O Schindler M Vigone

From the Department of Audiology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

An investigation was made of quotients of intelligibility with various types of signal/noise (S/N) ratio, using traffic noise at its actually recorded intensity

MATERIAL AND METHODS

The experiment was designed for road traffic noise. For this purpose, a tape consisting of the 1-minute recordings of daytime road noise, each taken at different points of Turin, wasu sed Its characteristics were

L_m dB	L_{eq} dB	σ + dB
88.8	89 4	2.35
L_m dB(A)	L_{eq} dB(A)	σ + dB(A)
71.6	73.1	3.54

This noise was fed through a Uher 4400 stereo 1C recorder to an Amplaid 500 audiometer calibrated in dB SPL, and then on to a loudspeaker Output levels corresponding to the figures given above were measured 3 m from the loudspeaker with a Brüel & Kjaer 2209 phonometer fitted with a 1613 octave filter

At the same time, Bocca s lists of two-syllable words recorded on an Amplifon disk were mixed with the road noise through an Amplifon 300 G5 audiometer and the Amplifon 500 Levels recorded in dB SPL on the audiometer were checked as already described

10 females aged 19-21 yr and 4 adults aged 40-50 yr were used. Each subject was placed 3 m in front of the loudspeaker in a soundproof room and required to repeat the words he heard in accordance with the classic rules of vocal audiometry Three lists of 10 words each were employed for each level Intelligibility was assessed as the mean of the three percents.

RESULTS

Table 1 shows the means obtained for each subject and for each S/N level

Table 1 *Intelligibility quotient for various S/N ratios (mean of three tests per subject and per ratio).*

Sound Noise Ratio	Young Subjects (18-21 yrs.)										Adult Subjects (40-50 yrs.)			
	B R	Ro P	Ri P	B L	P.P	G G	P.E.	P.M.	G.D	G.B.D.	O.G.C.	S O	B L	R.G
65 90	10	0	19	33	23	23	20	26	33	10	0	3	0	0
70 90	36	23	66	56	53	53	66	76	63	63	6	30	40	26
75 90	63	56	93	90	86	90	83	90	76	86	56	70	80	73
80 90	96	80	100	100	93	93	86	100	86	93	50	60	83	80
90 90	90	90	100	100	100	100	100	100	100	100	96	96	93	100
100 90	100	100	100	100	100	100	100	90	100	90	86	93	96	96

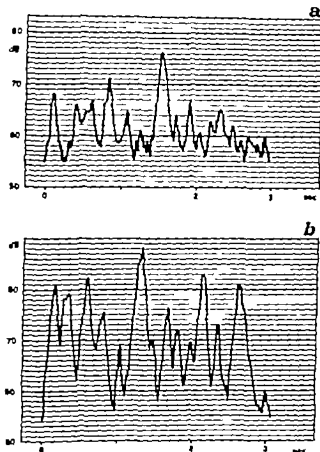


Fig 1 Graph of phonatory level without (a) and with (b) road noise.

the phonemes produced prevalently at articular level. This depends on the fact that the longer relative duration occurs in the former the approximate ratio with respect to the latter being 2 1

Further more than half the phonemes produced at prevalently articular level have decidedly lower levels than those produced prevalently at laryngeal level To conclude it can be broadly assumed that the levels of verbal expression are a function of laryngeal phonatory activity

CONCLUSIONS

The relative dimensions of the data would appear to be particularly significant as they indicate a difference of some 10 dB between the measurements without noise and those with

It should be pointed out that the experimental situation prevented autophony by the auricular airway which was impeded by the presence of the earphones It would perhaps have been useful, *in absolute terms to take measurements* in linear dB also remembering the considerable spectral component lower than 500 Hz. From *a communications point of view (see the results* of the sonographic research on phonemic emission) the component beneath 500 Hz is the *least important because it is masked by envi* ronment noise, particularly road noise

In biological terms, an increase of about 10 dB in the level corresponds to a much greater force because it is measured in terms of energy not of psycho-acoustic measurement This greater effort can be chiefly identified in the lungs which have to guarantee a ten-fold increase in expiratory pressure In this regard, corresponding spirometric measurements would be of interest, even though such operations are rather complex. Laryngeal effort is also considerably increased but direct evaluation is difficult Allowance should also be made for the fact that the lungs are not always capable of assuring the above energy increases so the increase in phonatory emission level is often compensated for by greater effort on the part of the intrinsic and extrinsic laryngeal muscles.

Electromyography might also be used for checking these data

In terms of possible damage at the level of phonatory effectors, we must not forget other *harmful non-auditory conditions represented by* stress factors and, particularly by the atmospheric pollution typical of road conditions *which electively affect all respiratory ways.*

From the communications viewpoint, an average absolute value of the order of 70-*75 dB (A) in verbalization conditions in the* presence of road traffic noise clearly indicates, if compared with road traffic values, what types *of signal/noise relationship occurs* in these conditions and particularly how rarely phonatory level reaches road traffic levels. This last point *is discussed separately* in the paper on the intelligibility of verbal messages.

Young subject responses

As can be seen from the standard deviation, these varied very little. The index of intelligibility (81.30 %) for the S/N ratio 75/90 i.e. normal speech, in the presence of traffic noise was reasonably satisfactory bearing in mind that two-syllable words were used. A considerable increase could undoubtedly be obtained with sentences or complete conversations (obviously at medium to high redundancy). Note should also be taken of the fact that the lists of words were spoken by a professional speaker at a less-than-normal speed. The index of intelligibility was 98 % at the S/N ratio 90/90 (speech and noise at the same level).

Adult subject responses

These were less uniform. However the group consisted of a mere four persons and cannot be used as a basis of definite conclusions. Comparison between young and adult subjects, in fact, was not contemplated as part of the research aim, but was considered as a first check on the data obtained for the young subjects.

Nervertheless, the curve for the adult subjects was distinctly different from that for the young subjects (fig. 1). At 70 dB, the index of intelligibility was only 25.5 %, i.e. useless as far as comprehension was concerned. Satisfactory values were obtained from 75 dB onwards. There was also a flexion of quotients on passing from 90/90 to 100/90 S/N. Experimentation on a larger series and the carrying out of conventional tonal and vocal audiometric tests (including central vocal tests) can state as a first approximation that adult subjects already display deterioration of the central acoustic pathway capacity, particularly of the ability to achieve optimum understanding of a message.

CONCLUSIONS

Our results offer a reference point for the evaluation of

- the intelligibility of various types of natural voice. Account must be taken of the frequent aphonia, dysphonias and phonasthenias that prevent a satisfactory phonatory level from being achieved at 75 dB
- intelligibility at various S/N ratios for subjects of different ages
- intelligibility at various S/N ratios on the part of subjects with various diseases of the CNS in the light of the more frequent epidemiological data
- the use of means for the amplification of speech signals that reach and surpass the levels of traffic noise.

It should, of course, be realised that the experimental conditions employed did not offer a true picture of what really occurs, since each electro-acoustic transduction and each passage through an electronic system leads to changes in and restrictions of the spectra. Both qualitative and quantitative variations are produced in both the signal and the noise. Lastly the overall atmosphere of communication is considerably affected by the reproduction of speech in a soundproof room. Discrepancies may also exist between the various systems and the measurement units for the acoustic levels.

Table 2. *Means and standard deviations (2 σ) of the intelligibility quotient values for the two groups (young and adult subjects).*

Sound/Noise Ratio	Young Subjects (18-21 yrs.) Mean Value	Adult Subjects (40-50 yrs.) Mean Value
65/90	18.80 ± 10.94	0.75 ± 1.50
70/90	55.50 ± 15.64	25.50 ± 14.27
75/90	81.30 ± 12.53	69.75 ± 10.07
80/90	92.70 ± 6.84	68.25 ± 15.88
90/90	98.00 ± 4.21	96.25 ± 2.87
100/90	98.00 ± 4.21	92.75 ± 4.71

Table 2 shows the means and standard deviation (2 σ) for the two groups of subjects.

Figure 1 gives the mean value curves for the two groups.

Figure 2 shows the response field for the young subjects as derived from the mean values and standard deviation.

Figure 3 shows this field for the adult subjects.

Two-syllable word levels were chosen to obtain values similar to those measured on speech with and without traffic noise in the preceding paper and to have S/N ratios equivalent to 0 and — 10 and + 10 respectively

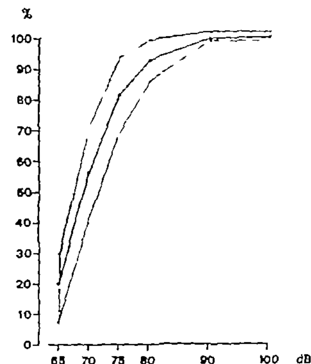


Fig 2 Percent intelligibility of lists of words (at different intensity levels) in the presence of road noise. Variability of response (dark band) on the basis of mean values and standard deviations (young subjects).

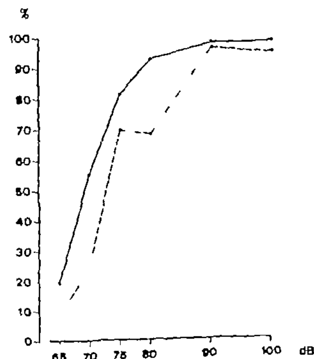


Fig 1 Percent intelligibility of lists of words (at different intensity levels) in the presence of road noise. Curves of mean values (——•—— *young subjects* — —•— adult subjects)

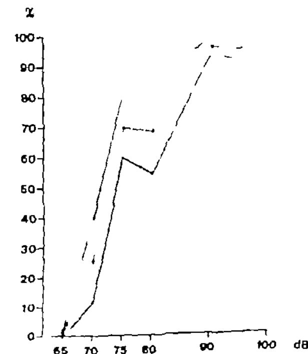


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Acta Otolaryng Suppl 339 44-54 1976

RESEARCH ON PHONEME EMISSION IN RELATION TO URBAN TRAFFIC NOISE

O Schindler

From the Department of Audiology University of Turin, Turin Italy

SCOPE OF THE RESEARCH

The purpose of the research is to evaluate the quality and quantity aspects of certain verbo-acoustic communication parameters in the presence of road traffic noise It is a well known fact that verboacoustic communication must take account of the perceptive integrative and executive sectors of the communicating partners as well as the characteristics of the channel between the partners

The overall problem involves a vast number of parameters (all inter related) and it is obviously out of the question to consider them all here We will also give brief mention to the relative catalogue using this also as an index of research approaches that should form part of a verboacoustic communication programme in a noisy environment The interest of this type of communication is of fundamental importance since for the moment and presumably for a long time to come the physiological state (meaning the statistical norm) of verboacoustic communication implies a very noisy background This is why for biologico-communicative economy purposes the parameters of verboacoustic messages certainly change to adapt to a much different situation from that pertaining during the long period that terminated only a few decades ago in which the quantity/quality of background noise fostered quite another system of verboacoustic communication

Perceptive sector parameters

Auditory evaluation of the various types and extents of pathology of the hearing system in relation to the translation and optimization of an acoustic message with a given S/N ratio.

Extra-auditory as communication is a global event, it is important to evaluate non-acoustic messages (particularly optical and vibratory other than chemical) in relation to their reinforcement or disturbing effect on the information channelled through the acoustic message It is therefore clear that the physiology and pathology of the non-auditory sensory sistems must be evaluated

Integrative sector parameters

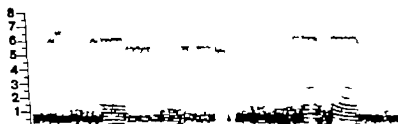
It is evident that the above mentioned modifications in messages with respect to perceptive parameters are upset at integrative level and in view of the considerable rise in peripheral message total bit/sec which largely exceed the maximum processing capacity of the human communications system a new choice strategy is called for

We would undoubtedly attribute the message optimization phenomenon to the integrative sector also even though it still belongs to the perceptive sector (central sensory ways) At this point we must also examine message profile and its breakdown into various channels, each of which has its own signal/noise ratio

Here too we should evaluate the semiotic and semantic data relating to signal and noise so as to establish the redundancy of the message which in our opinion ought to be increased as a result of the data presented above with respect to the specifically verboacoustic aspect and globally as a result of reinforcement through the extra-acoustic channels







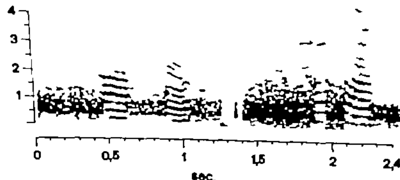


Fig. 1 (babbo papà) Excellent preservation of owel structures as regards their parameters of fundamental frequency formants and transitories. Poor consonant reading. Specifically explosion noise is only heard on the first P of papa. The ocal bar of oiced occlusives not identifiable. Explosion peaks of B's easily identifiable on the level curves.

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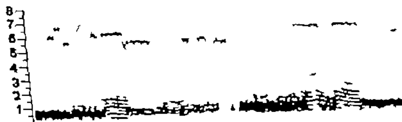
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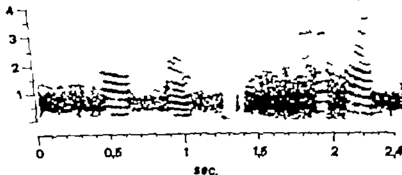


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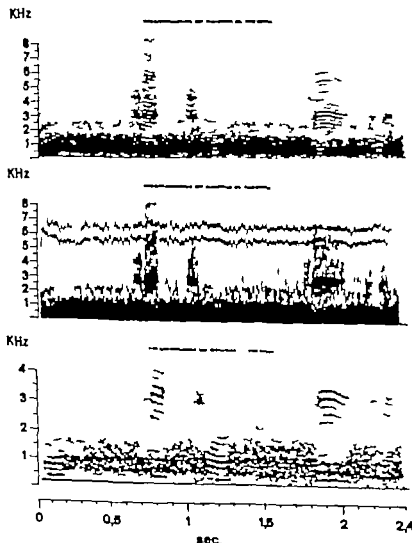


Fig. 4 (occio gigl). Very good vowel phoneme preservation in all parameters. Considerable deterioration of consonant phonemes of which only the constrictive component (including vocal bars is legible) while the occlusiv component is quite illegible.

Executive sector parameters

Again, at message production level, we shall ha e to evaluate the communications profils in at least three main sectors

— erbal
graphico-pictorial
— mimico-gestural

Substantially we are in the presence at verbal level of an attempt to offset an unfavourable S N ratio by ncreasing phonatory level. As this has evident upper limits (see also the results of the other two *researches* in this group), other compensating factors at executive level inevitably are triggered over and above the redundancy compensations that do not belong to this sector and in addition to the modifications (slowdown) in verbal flow

Emotive-relational sector parameters

It is a well-known fact that as communication is a social phenomenon it depends on the choice of a common code between the partners, on the learning of this code (developmental biology) and on the emotive-relational state of the communicating group and its components.

Interindividual channel parameters

This concerns evaluations of the external environment in relation to all types of communi-

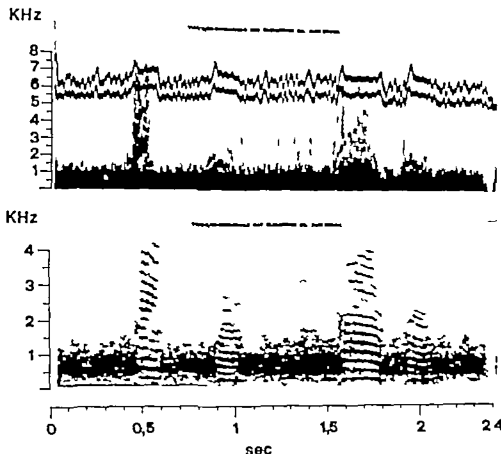


Fig 2 (tetto dado) The various parameters of the vowel structures well preserved. Greater deterioration of consonant structures. Explosion noise detected in all cases (including on the level curves). A hint of vocalic bar on the second D of dado

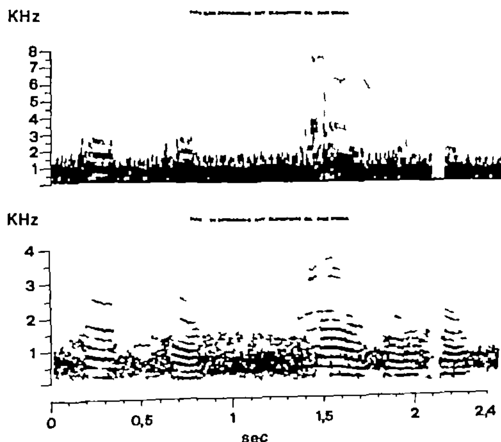


Fig 3 (cocco lago). Vowel structures well preserved in all parameters. Greater deterioration of consonant structures. Explosion noise in two out of three cases. Explosion peak present in the three cases. Vocal bar hard to pick out on the G

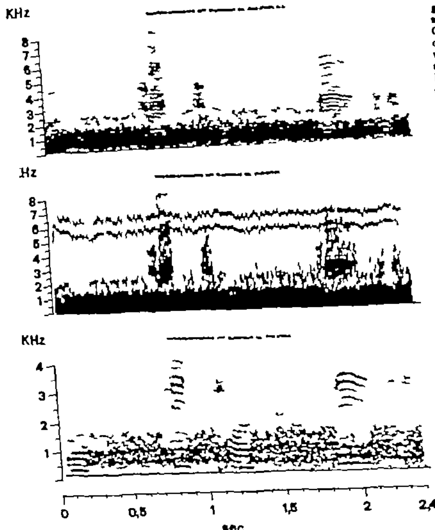


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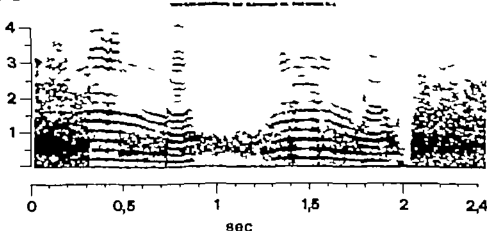
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Fig 5 (mamma nonna). Good preservation of vowel phonemes in all parameters. Consonant phonemes also well preserved, particularly the harmonic structure of nasal resonance (more evident on the N's than on the M's). Explosion noises not evident on the M's, but evident on the N's.



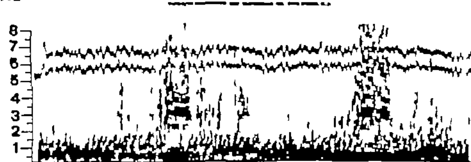
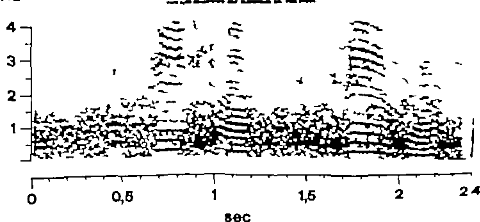
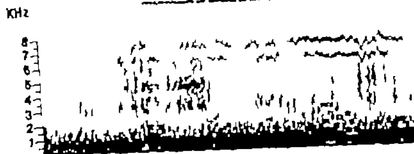


Fig 6 (fifa vi a). Good preservation of vowel phonemes in all parameters. Very bad preservation of consonant phonemes which are partially confused with traffic noise. The harmonic sonarization components of the V almost illegible. The harmonic structure preceding FIFA is made by a car horn.





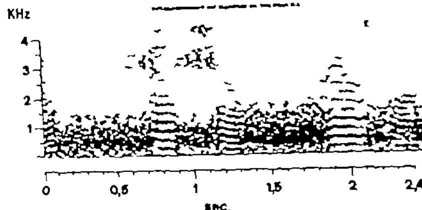
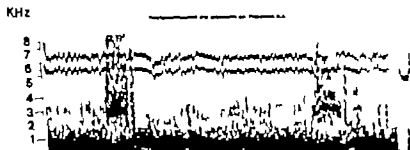


Fig. 7 ([illegible] rosa). Very good preservation of vowel phonemes in all parameters. Good preservation of consonant phonemes. Sonorization of the S in rosa not legible.



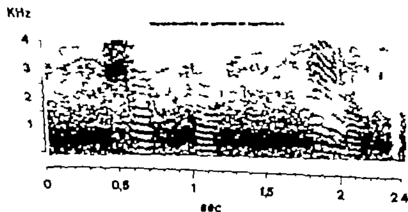


Fig. 8 ([illegible] zia). Very good preservation of vowel phonemes in all parameters. Very good preservation of SC phoneme parameters. Poor preservations of phoneme Z parameters and it is hard to distinguish any constrict component structure.

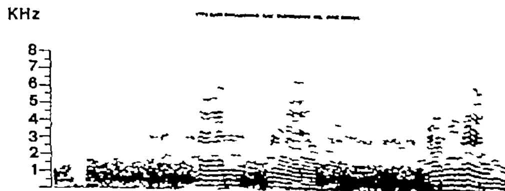
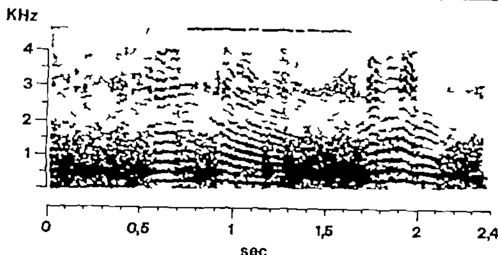


Fig 9 (zanzara lulu). Very good preservation of the vowel structures in all parameters. Very bad preservation of the Z structures apart from some sonorization. Good preservation of L structures.





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MATERIAL AND METHODS

This section covers a qualitative-quantitative but prevalently qualitative electroacoustic analysis of phoneme material produced directly in road traffic. A young woman trained to articulate *clearly (she is a logopaedist)* was made to repeat a list of words in a street where traffic noise was considerable The list of words corresponds to that normally used at our Department for the analysis of phonemes produced by logopathic patients Here it is

papà babbo tetto dado cocco lago
ciccio gigi mamma nonna fifa viva
sasso rosa sciocco zia zanzara lulu
ramarro rana giugno luglio strada
spruzzo taxi

It comprises all phonemes in the Italian language in the body of words. Although the various items have a semantic content classing



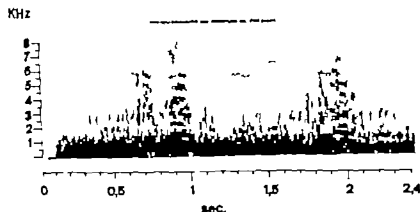
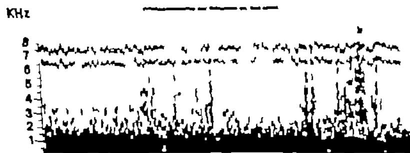


Fig. 10 (ramarro rana). Very good preservation of vowel structures with respect to all parameters. Good preservation of R structures.



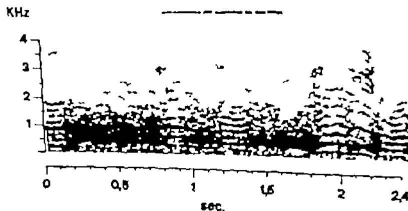
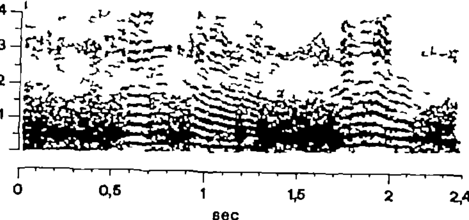


Fig. 11 (giugno luglio). Very good preservation of vowel structures in all parameters. GN structure preservation not good, better but still not good the GL structures.



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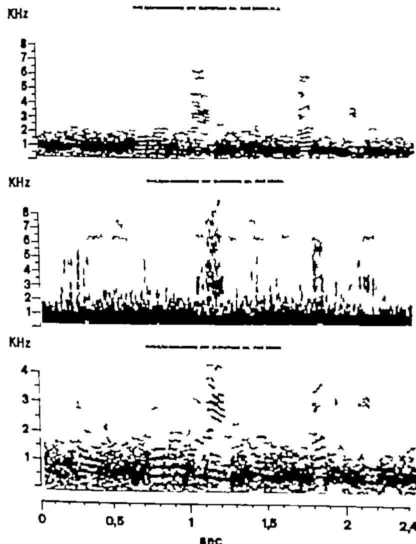


Fig 13 (completo text) Very good preservation of vowel structures in all parameters. Preservation of MPL group structures not good although the M and L components are legible. Structures of the CS group very badly preserved (including the constrictive component).

3) Wide band analysis with frequency spectrum from 80 to 8000 Hz

4) Analysis of level curves (normal and —10 dB) level curves are always compared with narrow and wide band analyses with frequency spectrum from 80 to 8000 Hz.

RESULTS

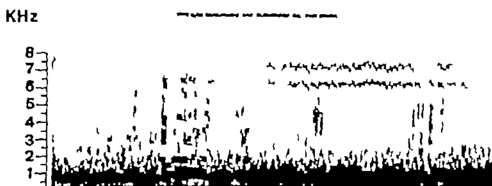
Result of the analyses are shown in the captions from figs. 1 13 Synthesizing the results, the following remarks can be made

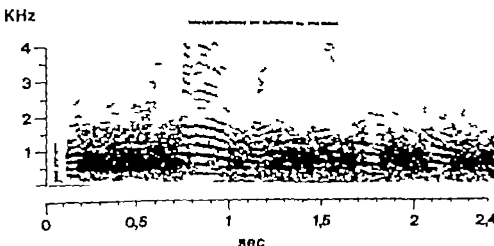
— The road traffic noise spectrum disturbs the reading of phonemes a great deal up to 1000 Hz disturbance is decidedly less from 1000 to 2000 Hz and practically non-existent from 2000 to 8000 Hz. It should also be borne in mind that at auditory level, the disturbance tends to shift towards acute frequencies by reason of the masking effect of low pitched frequencies.

— The level, frequency and spectrum suprasegmentary gross dynamics, in other words the rhythmic structures of the phrase are sufficiently well preserved. A marked slowdown in verbal flow i.e. in the number of phonemes per unit of time, should be noted. This occurs prevalently by way of the lengthening of vowel phonemes and constrictive conso-



Fig 1 (strada sporca). Very good preservation of vowel structures in all parameters. Poor preservation of STR and SPR group structures best preservation seen in constrictive and liquid component





them as physiological rather than artificial they can be considered in practically the same way as logatomes given their brevity and the fact that they are not connected within a sentence

The chosen road was via Genova running alongside Turin's General Hospital (Molinette Section) This is a road of average width (about four cars side by side) used by public (including trams) and private traffic. It is flanked both sides by buildings, the distance between them being about three times the width of the carriageway

Measurements were taken at 11 a. m. when traffic flow is at its average day time level The noise level and spectra were on a par with those used on tapes in the other two researches. In view of the prevalently qualitative character of the study we did not consider it necessary to investigate the quality-quantity aspects of road traffic noise at the point in question

The repeated words were recorded on a Uher 4400 Stereo Report I C recorder and then analysed electroacoustically with the Sonograph Kay

The following types of analysis were undertaken

1) Narrow band analysis with frequency spectrum from 80 to 8000 Hz
2) Narrow band analysis with frequency spectrum from 80 to 4000 Hz

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URBAN TRAFFIC NOISE, CARDIOCIRCULATORY ACTIVITY AND CORONARY RISK FACTORS

L. Verdun di Cantogno R. Dallerba, P.S. Teagno, L. Cocola

From the Department of Audiology and the 1st Department of Medical Patology University of Turin, Turin, Italy

SCOPE OF THE RESEARCH

The aim of this research was an assessment of the effect of road noise lasting 10' on cardiocirculatory activity and various blood chemistry indices, particulary those apparently associated with the pathogenesis of arteriosclerosis. Normal, dysmetabolic and coronaropathic subjects were examined.

While it can readily be appreciated that certain stimuli can act on the cardiovascular apparatus, leading to changes in the work of the heart and its performances, it is less easy to understand how certain psychological and emotional conditions, or certain sensorial stimuli completely mediated by the CNS influence the heart and its vessels, thus supporting atheroma, endoarterial thrombosis or serious arrhytmias.

Acoustic stimuli offer an ideal method for the study of effects mediated by the CNS, since they can be exactly reproduced and measured in the absence of every other factor likely to influence cardiac frequency and arterial pressure, or left ventricular performance as assessed by simultaneous ECG phonocardiographic and carotid pulse recordings. Attention was also given to the blood chemistry indices known as related to coronary risk factors. Direct evaluation of catecholamine levels was not attempted, because this technique gives widely scattered results, even under normal conditions. Urinary catecholamines excreted during the test were however taken into consideration. The limitations of this method are well known.

MATERIAL AND METHODS

The absence of literature data concerning the effect of traffic noise on the parameters chosen for study suggested the advisability of preceding the experiment by a series of investigations of the effect of white noise and speech noise (100 dB and 80 dB intensity continuous stimulation for 10' or for 1' followed by an interrupted stimulation for 9') in 16 subjects, *to determine the* effect of noise of different spectrum and intensity administered with different modalities. This preliminary study (details in the press) showed statistically significant differences between stimulated and control subjects. We therefore began by exposing 33 subjects aged 20-70 yr to road noise. A further 11 normal subjects (mean age 7 yr) were studied for comparison, i.e. they were subjected to all the experimental procedures in the absence of road noise (control group).

Prior audiometric examination showed that all subjects had normal hearing for age. Only male subjects were examined, so as to ensure that responses were not affected by neurohormonal and neurophsychic factors pertinent to the two sexes.

The patients were divided into 3 groups (11 normals, average age 36.7 yr 11 diabetic or dyslipaemic, average age 46.4 yr 11 coronaropathic, average age 52 yr). As already stated, the average age of the 11 controls was 27 yr. A division was also drawn between subjects aged more and less than 45 yr., i.e. 17 (mean

nant phonemes as it is evident that occlusive consonant phonemes cannot be lengthened These data implicity lead to some rhythm modification

— Vowel structures are well preserved with respect to all vowel phonemes and all their parameters (harmonic, melodic dynamic structure, formant and transitory structures) It should however be recalled that these remarks apply if laryngeal function is good, for if laryngeal emission is affected by pathological factors, the sound structure is transformed partially or wholly into a noise structure and the readability of vowel phonemes deteriorates drastically

— Occlusive consonant structures (P B M T D N K Gh Gn) are badly deteriorated

The following parameters are considered in particular

— pre-explosion quiet deteriorated because it is filled with traffic noise which also wipes out sonorization of sonant orals (there is practically no vocal bar) By contrast, sonorization of nasals (with the sole exception of Gn) is well preserved

— explosion noise detectable as such in a differentiated way

very poor for bilabials
good for linguoalveolodentals
fair for dorsivelars.

A similar situation although more favourable is evident reading level curve peaks.

— Formant transitories with preceding and following vowels satisfactory in all cases less satisfactory with the first formant and more the higher the frequency of the second formant In conclusion reading of these consonants may be summarised in the following table

poor P B K Gh
average Gn T D
good M N

— Constrictive consonant structures (F V S S Sc, Gl L, R) are adequately preserved on the whole

Liquids and vibrants are best preserved (providing they are not in the body of consonant groups). The following remarks can be made about the remaining constrictives

— Formant areas are clearly readable as regards phonemes S Ş and Sc, and very poorly readable as regards F and V

— V and Ş sonorization is badly deteriorated

To conclude reading of these consonants may be summarized in the following table

poor F V
average S
good L, R Gl Ş Sc

— Semiconstrictive consonant structures (Z, Z, $C_{()}$ $G_{(I)}$ are all badly deteriorated particularly as regards their respective occlusive components.

— The structures of consonant groups (STR, SPR and MPL only were considered) are badly deteriorated in any case deterioration of the group is much greater than the sum of deteriorations of phonemes considered in isolation

— As a final consideration we might say that broadly speaking, most affected are those phoneme structures that carry the greatest *quantity of information (consonants, particularly occlusives)*

CONCLUSIONS

Comprehension of messages in environments containing road traffic noise will be considerably deteriorated with respect to individual phonemes and isolated words with low resonance whereas comprehension of long segments (sentences and groups of sentences) is satisfactory Furthermore comprehension increases with message redundancy

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57.3 yr) and 16 (mean 32.7 yr) respectively excluding the controls.

Fifteen minutes after being settled on a bed in an Amplifon standard G5 silent booth erected in a room lined with soundproof panels, each subject was exposed to a tape consisting of 10 one minute recording of traffic noise registered at 10 different points in Turin Its characteristics were

L_m dB	L_{eq} dB	$\sigma +$ dB
88 8	89 4	2.35
L_m dB (A)	L_{eq} dB (A)	$\sigma +$ dB (A)
71 6	73 1	3 54

This noise was fed through a Uher 4400 Stereo Report 1 C recorder to the circuit of an Amplaid 500 Audiometer calibrated in dB SPL, and then to the subject s headphones. It was used at its true intensity which was checked with a Brüel & Kjaer phonometer fitted with a model 1613 octave filter

Neither the normal nor the control subjects displayed basal changes in blood chemistry para meters in blood pressure or in electrocardiographic and phonocardiographic patterns. Each patient had been fasting for at least 6 hr Five blood samples were taken as follows 20 and immediately before stimulation — the arithmetical mean of these values was used as the " basal value — 10 when the tape stopped and 30 and 90 after it started To avoid problems of stress related to the blood samples a butterfly needle was used kept patent with saline

There was no significant difference between the two basal values, bearing in mind the scatter displayed by these data under physiological conditions Sugar insulin uric acid, total lipids, cholesterol and triglycerides were measured in each sample using the following methods

— Blood Sugar Enzymatic determination with G6-PD-hexochinase (Biochemica test combina tion kit)

— Blood Insulin Richter radioimmunological kit utilizing a Packard " Tricarb Liquid Scin tillation Spectrometer

— Blood Uric Acid " Urica Quant " colorimetric enzymatic method (Biochemica Test Combination)

— Total Lipids Colorimetric method of Zoellner & Kirch

— Cholesterol Biochemica Test Combination Kit according to D Watson B Zak and H H Lefler

— Triglycerides Enzymatic determination of serum concentration with Biochemica Test Combination Kit

— Urinary Catecholamines were determined fluorimetrically immediately before and imme diately after the examination so that their excretion during the test could be known by their concentration in the samples.

Blood pressure was measured before during and after the stimulation with road noise 0-1 2 3-4 5-6 7 8 9 10 11 12 13 20 30-60 90 with an Erka " Diasist apparatus, using a pneumatic cuff fitted with a microphone for the registration of Korotkoff tones. Systolic and diastolic pressure values were automatically in dicated every minutes on dials with a margin of error of less than 1 5 ‰.

ECG and polygraphic data were obtained with a 8-channel Elema Schönander Mingograf 81 " giving a simultaneous ECG 4-fre quency phonocardiogram and carotid pulse re cording Polygraphic records were taken at the same intervals as those used to record arterial pressure Examination of the ECG phonocar diogram and carotid pulse data gave and indication, inter alia of cardiac frequency The distance in terms of time and the relation between certain features of the heart cycle shown by these recording were than calculated so that the influence of the traffic noise on the heart performance could be detected and studied

The following systolic times and indices were considered

— LVET (left ventricular ejection time) from the foot of the ascending branch of the carotid sphygmogram to its dicrotic incisure)

— $S_1 S_2$ (mechanical systole) from the 1st component of the first sound to the aortic component of the 2nd sound

— PEP (pre-ejection period or tension time or pre-expul ion systole) from the start of the Q wave to the foot of the ascending branch of the carotidogram, less the PTT

— PTT (pulse transmission time) fr m the

aortic component of the 2nd sound to the dicrotic incisure of the carotid pulse.

— Q S_1 (Total or electomechanical systole) from the start of the Q wave to the first component of the 1st sound.

— Q_1-S_1 (deformation time) from the start of the Q wave to the first component of the first sound.

— ICT (isovolumetric contraction time) from the first component of the 1st sound to the foot of the ascending branch of the carotid sphygmogram, less the PTT

— PEP/LVET expresses left ventricular performance, LVET/ICT seems more closely related to myocardial contractility

The arithmetical mean of 10 beats was calculated for each systolic time corrected for frequency and compared with the normal theoretical values, to obtain significant data on myocardial performance. In addition, the product of cardiac frequency with systolic arterial pressure offers a good indication of coronary flow and myocardial oxygen needs.

RESULTS

The data were expressed as percents of the initials values referred as 100 and analyzed by applying Student's interval estimation with P = 0.05 The controls were compared with each of the three groups and with the stimulated series as a whole Comparison was also made between subjects aged less and more than 45 yr

After illustrating the pattern displayed by each parameter separately an account will be given of their behaviour in normal, dysmetabolic and coronaropathic subjects.

BLOOD CHEMISTRY PARAMETERS

Sugar

Road noise brought about an immediate increase in blood sugar This was more evident (over 50 of cases) in coronary and dysmetabolic patients (Fig. 1). At 30 values were still high in 50 of the normal subjects probably because they were younger Values, in fact, differed significantly in function of age at 30' and 90' (Fig. 2).

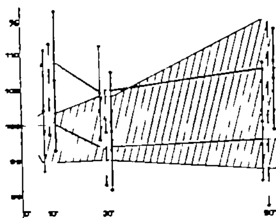


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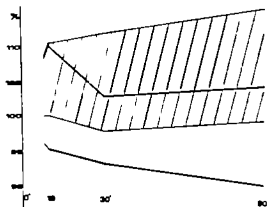


Fig 2 Blood sugar Subjects aged between 20 and 45 yr ///////// Subjects aged between 46 and 70 yr ═══

Insulin.

Traffic noise was accompanied by a marked increase in band width in both normal and dysmetabolic subjects. This was more evident at 90' especially in the normal cases (Fig. 3). At the end of the test, levels were well up in about 80 / of normal and 50 / of dysmetabolic subjects, whereas they were down in 50 / of the coronary group. This, once again, may be attributed to age, since a marked, late rise in blood insulin is typical in younger subjects (Fig. 4).

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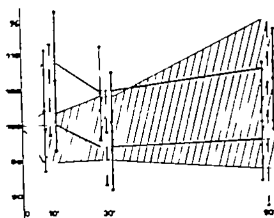


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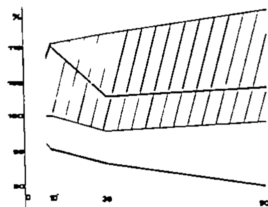


Fig 2 Blood sugar Subjects aged between 20 and 45 yr ////////// Subjects aged between 46 and 70 yr ═══

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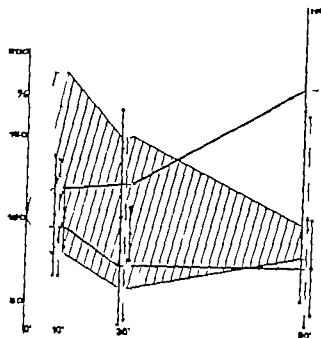


Fig 3 Serum insulin. Normal subjects ———● Dysmetabolic subjects ★——●——★ Coronary patients O———O Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects

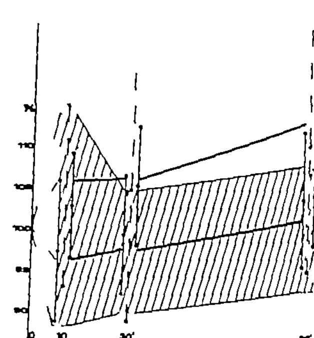


Fig 5 Total lipids. Normal subjects ●———● Dysmetabolic subjects ★——●——★ Coronary patients O———O Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects

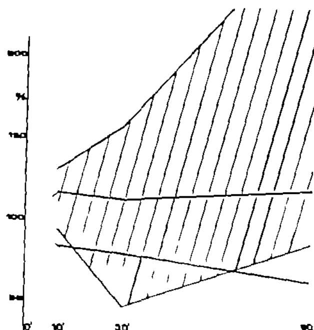


Fig 4 Serum insulin Subjects aged between 20 and 45 yr ////////// Subjects aged between 46 and 70 yr

Total lipids

At 30 and 90 both coronary and dysmetabolic subjects displayed an increase in blood lipids. Band values expanded to a much greater degree in the dysmetabolic than in the other groups (Fig 5) In the normal subjects values were comparable with these observed in the controls. No significant differences in function of age could be made out

Triglycerides

Road noise caused a fall in values that appeared earlier (10 and 30') in the dysmetabolic as opposed to the coronary subjects. At 90 there was an increase of band amplitude in the normal group (Fig. 6) The fall at 30 was more marked in patients over 45 yr (Fig 7)

Blood cholesterol

Values increased after 30 and 90 in about 50 of the normal subjects. Increased band amplitude was noted from the start especially in the coronary patients (Fig. 8) There was no significant difference in function of age

Uric acid

A marked increase was observed at 30 and 90 especially in the dysmetabolic group (Fig 9) Band amplitude also increased at an early stage in the coronary subjects, and later in the normal group Up to 30 increases were higher in the younger subjects (Fig. 10).

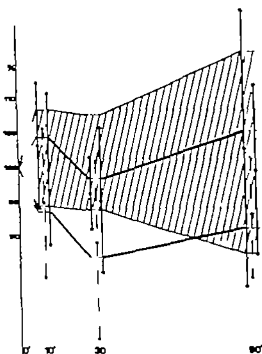


Fig 6. Triglycerides. Normal subjects •———• Dysmetabolic subjects ★——•——★ Coronary patients o———o Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects ═══

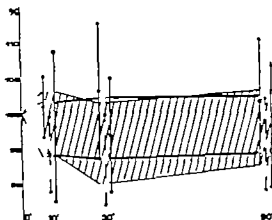


Fig 8 Blood cholesterol. Normal subjects •———• Dysmetabolic subjects ★——— ———★ Coronary patients o———o. Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects ═══

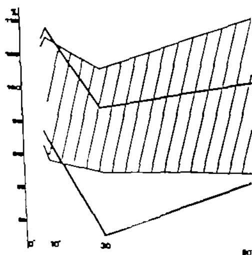


Fig 7 Triglycerides. Subjects aged between 20 and 45 yr ////////// Subjects aged between 46 and 70 yr ═══

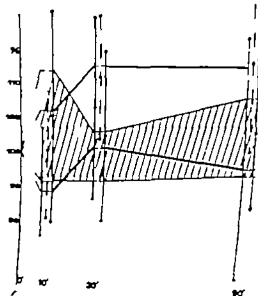


Fig 9 Blood uric acid. Normal subjects •———• Dysmetabolic subjects ★——— ———★ Coronary patients o———o. Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects ═══

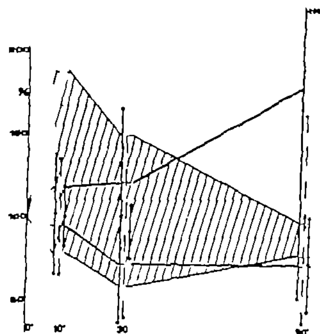


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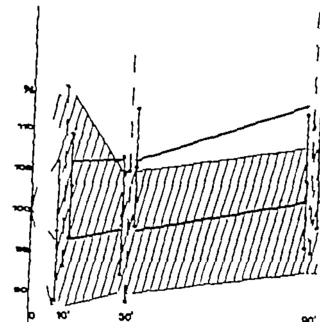


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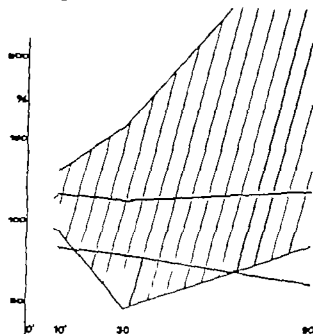


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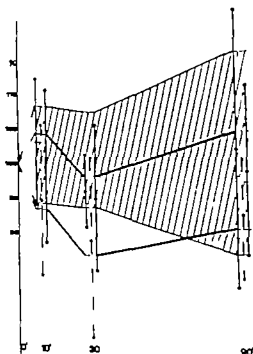


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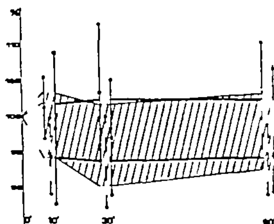


Fig 8 Blood cholesterol. Normal subjects •——• Dysmetabolic subjects ★—— ——★ Coronary patients O——O. Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects ══════

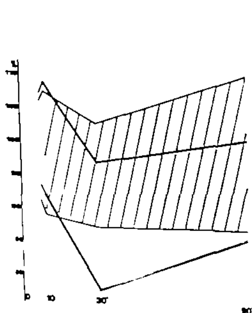


Fig 7 Triglycerides. Subjects aged between 20 and 45 y ////// Subjects aged between 46 and 70 yr ══════

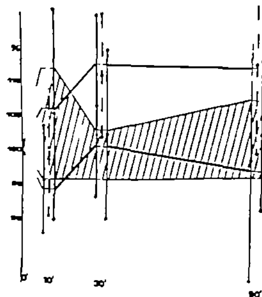


Fig 9 Blood uric acid. Normal subjects •——• Dysmetabolic subjects ★—— ——★ Coronary patients O——O. Range of variation in unstimulated subjects ////////// Range of variation in stimulated subjects ══════

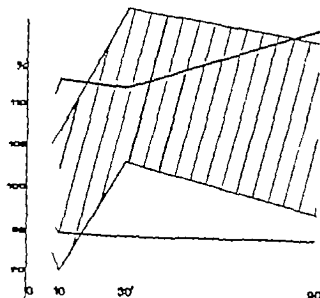


Fig 10 Blood uric acid. Subjects aged between 20 and 45 yr ////////// Subjects aged between 46 and 70 yr — — —

Catecholamines

Values observed before and after the test are shown in Table 1 To obtain more accurate data it would have been necessary to keep the subjects completely at rest for 24 hr before and after the test. This, however was not possible In spite of their limitation the data showed that road noise enhanced catecholamine excretion in the dysmetabolic group The relatively slight entity of the stimulus and its nature lead one to suppose that nothing less than direct haematochemical determination of the catecholamine content would have given an accurate picture of this parameter The techniques required however are difficult to apply in vivo since very low quantities are involved Furthermore catecholamines are very rapidly inactivated in the body

ECG AND HEART PERFORMANCE

Road noise did not lead to any significant ECG changes, even in subjects with marked basal signs of chronic or sub-chronic myocardial ischemia During the course of the experiment isolated atrial or ventricular extrasystole were observed in some subjects, though these appeared to be devoid of particular significance

Left ventricular performance was indirectly assessed polygraphically by simultaneous ECG phonocardiographic and carotid pulse recording Comparison was made between the length of the PEP and LVET and of the relative importance on the ICT with respect to the initial DT The reciprocal relation between these parameters are indirect pointers to heart performance, especially as far as possible ischemia of the cardiac fibers is concerned Our results did not reveal any marked variations in these and in other parameters. The noise used was apparently insufficient to influence these indices to an appreciable extent

Changes in cardiac frequency were considered separately and together with systolic arterial pressure As already stated frequency times systolic pressure is regarded as one of the best pointers of coronary flow tension time index and myocardial oxygen consumption Traffic noise was responsible for a distinct increase of this index in the normal subjects, followed by a fall in response during the application of the stress (Fig. 11 A) A somewhat similar pattern was noted in the dysmetabolic group, though here values remained significantly high in 50 of cases until the end of the noise, after which there was a certain widening of the band (Fig. 11 B) In the coronary patients the increase was significant for a longer period in a larger number of cases (Fig 11 C)

CONCLUSIONS

Exposure to road noise in the form employed in our experiment was followed by enhancement or depression of several blood chemistry parameters, or a wider scattering of their values, as shown by an increase of band amplitude around a more or less unchanged mean On many occasions both responses were present though their relative importance varied Blood sugar displayed the earliest changes by contrast with the late response observed in the case of blood insulin

We were particularly struck by the extent of the blood uric acid response showing that noise has an effect on the metabolism of nucleic acids. As was to be expected normal subjects generally presented less significant changes, especially in total lipids and triglycerides. An immediate increase in blood sugar was noted only in 50 of this group as opposed to 80 of the others,

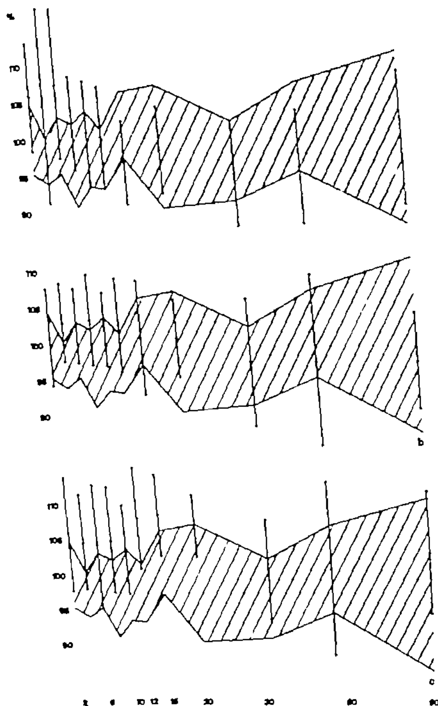


Fig. 11 Cardiac frequency times systolic arterial pressure: a) Normal subjects •———• b) Dysmetabolic subjects •———• c) Coronary patients •———• ( ) b)) Unstimulated subjects ////////

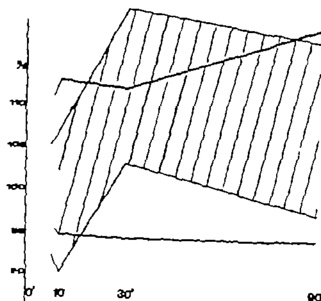


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Our blood chemistry data are to scanty to permit full interpretation of the changes observed. It can, however be stated that road noise of the type employed can lead to distinct changes in all the parameters taken into consideration these being of great importance as coronary risk factors in general terms, and as tending to support atheroma.

Table 1 *Catecholamines excreted by patients before and after the test Values in μg*

CATECHOLAMINES											
Controls (1)			Normal subjects			Dysmetabolic subjects			Coronary patients		
Subject	1st with-drawal	2nd with-drawal	Subject	1st with-drawal	2nd with-drawal	Subject	1st with-drawal	2nd with-drawal	Subject	1st with-drawal	2nd with-drawal
56	8.5	7.5	31	10	5.5	32	3.23	9.20	35	( )	( )
60	11.25	10 45	33	18	20	40	12.6	9 6	38	6.3	5 4
62	8 4	13	34	13 12	( )	43	(*)	(*)	41	( )	19.5
63	16.8	18	36	17 4	13.5	47	10.2	5	46	14 8	13.2
64	9 1	10.5	37	16	12 6	48	4.55	13 65	47	10.2	5
			39	10.4	14	50	11.2	27..	54	7.2	13
			42	16.15	10.20	51	23 4	28.9	55	7	1 9
			44	( )	( )	53	7 8	8.04	58	20	16.19
			45	4.25	8 1	57	4.8	6.44	59	7.5	6.2
			49	10.5	12.15	61	( )	( )	67	15	18
			65	11.25	6	66	3 85	7.2	68	3 85	7.2
Mean value	10 81 – 100	11 89 – 109 99	Mean value	12 7 – 100 %	11.33 – 89.2	Mean value	9 07 – 100 %	13.67 – 150.7%	Mean value	10.22 – 100 %	9.89 – 96.77 %

(1) Urine samples were attained from only 5 of the 11 controls
( ) Missed diuresis of subjects.

whereas the late insulin response was more marked and frequent. This was the only group to display a late increase in cholesterol values, while its changes in uricemia included both, decreases and increases, leading to an over 100 / enlargement in band amplitude at 90'

Diabetic and dyslipaemic subjects presented the most significant changes in total lipids, triglycerides and uric acid. This group displayed the most evident and erliest (10' and 30') fall in triglycerides, by contrast with the increase in total lipids and their wider band amplitude at 30' and 90'

Coronary patients showed a similar pattern, though apart from blood suger their changes were less striking. In this group the main fea tures were variations in band amplitude, except in the case of total lipids, whereas triglycerides values shifted less than in the dysmetabolic subjects, but earlier than in the normal group

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Acta Otolaryng Suppl 339 64 1976

URBAN TRAFFIC NOISE AUDITORY AND EXTRA AUDITORY EFFECTS

Concluding remarks

G Rossi

From the Department of Audiology University of Turin Turin Italy

In this series of papers we have given particular attention to the effects of traffic noise on features of the auditory function verbo-acoustic communication, some phenomena associated with the activity of the central nervous system and the cardiocirculatory apparatus.

The question of the effects of road noise has been examined for the first time in such a way as to allow albeit through no more than partial findings, an overall view of a situation that faces each of us day by day Some very interesting data have emerged and further research is under way to examine them more closer This was also be extended to cover other questions, such as the secretion of certain hormones, a subject that appears to have been overlooked so far

The question examined in these papers is of importance and its evaluation involves the assessment of traffic noise as a factor in modern life, and of the as yet unestablished consequences that it may have under certain conditions, on the physiological dwindling of sensory performance in function of age as well as the onset of various morbid signs that are by no means the prerogative of senescence

Our results must of course, be read in the light of the spectral composition of the noise and in the light of the methodological approach employed in the experiments. Any form of generalization would be out of place With this warning against the drawing of general or absolute conclusions in mind however it seems safe to hazard the suggestion that the noise produced by road traffic is not without its effects on various functions and activities performed by man This is of particular significance to those who work in noisy surroundings and what is more fail to find outside such surroundings the conditions that would enable them to recover their lost physical and psychological energies

In the light of our at present fragmentary knowledge, the enunciation of a detailed programme for the solution of this question would be both illogical and premature Yet one would, perhaps, be not too far of the mark with respect to the real terms in which the question of pollution in the form of traffic noise presents itself if one were to postulate its solution through combined efforts in the field of mechanical engineering and urbanistic technique and regulation designed to reduce the production of noise as far as possible and on the other hand to discipline traffic in such a way as to take into account the data and models provided by phonometry and their elaboration Initiatives of this kind must of course be flanked by carefully thought out and severely applied laws, coupled with the due instruction and sensitization of public opinion through advertising

No effort must be left unspared, since that a reduction, however slight, in the present intensity of the noise produced by road traffic would help to diminish the harmful effects it causes in man, one reason for which is its characteristic continuity

amplaid 702

compliance and acoustic reflex meter

Compliance
Contralateral reflex
Ipsilateral reflex

direct reading compliance meter in cc

pressure range from — 600 mm H_2O to + 600 mm H_2O with automatic pressure limiter

digital store of maximum compliance value for executing acoustic reflex measurements

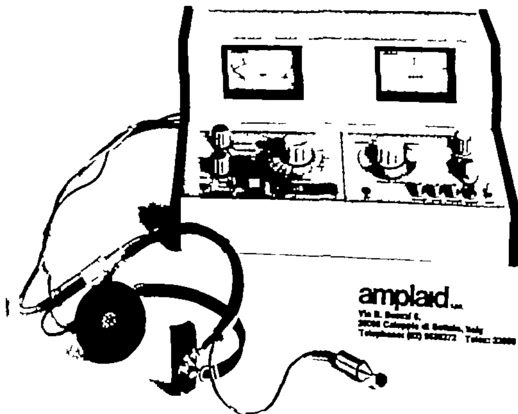
entirely linear calibration of input/output function over the entire compliance range (0 to 5 cc)

direct reading reflex meter in % variation of the maximum compliance value

for contra- and ipsilateral reflex eliciting, pure tone stimuli (0.5, 1, 2, and 4 K Hz) and broad band noise as well as low- and high-pass filtered noise

miniprobe incorporating all transducers and large selection of tips to fit all ears

output to X-Y plotter and strip-chart recorder



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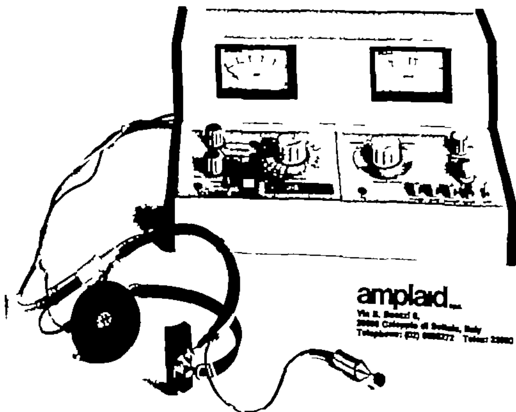
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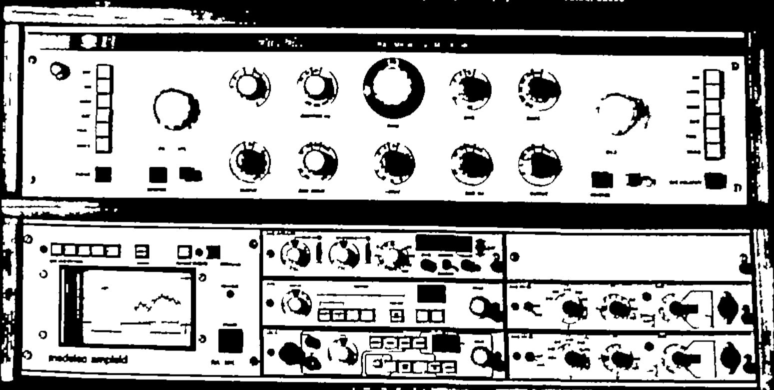
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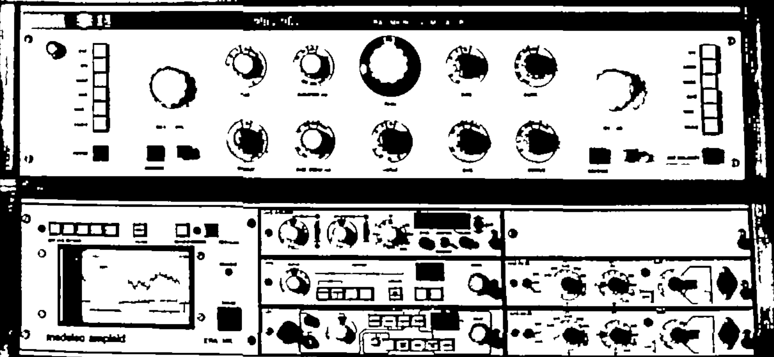
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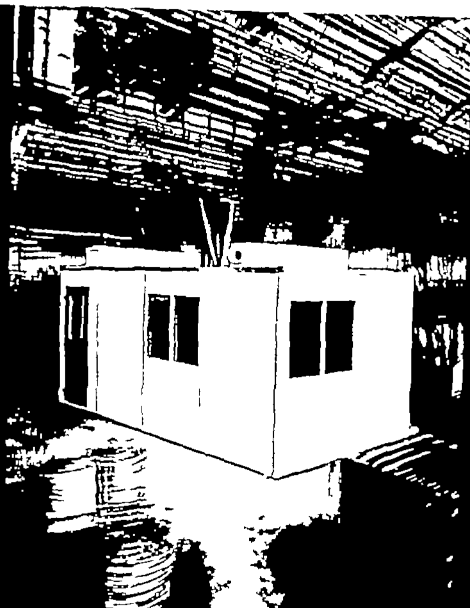




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ACTA OTO LARYNGOLOGICA

SUPPLEMENT 331

Cochlear Action Potentials in Experimentally Induced Hypothyroidism in Guinea Pigs

BY

M RUBINSTEIN M D T P PERLSTEIN M A
and M HILDESHEIMER M A

From the Department of Otorhinolaryngology
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Venice, May 21–25 1973

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Introduction

The correlation of hearing disability and hypothyroidism has been made by many observers. Kemp (1907) was the first to describe a case of acquired hypothyroidism with associated deafness. Similar descriptions reporting cases with acquired hypothyroidism and associated deafness appeared later (King, 1907; Moehlig, 1927). A conductive hearing loss was reported and the cause was attributed to a myxedematous middle ear (McMahon, 1947). Recently utilizing more precise hearing tests, most of the hearing loss was shown to be of a sensorineural type, sometimes with an additional component of the middle ear forming a mixed type of hearing loss (Howarth & Lloyd, 1956; Hilger, 1956; Ritter & Lawrence, 1960; De Vos, 1963). Hearing disability seems to appear only in a certain percentage of the patients with proven hypothyroidism. Post (1964) reported forty-two patients with proven hypothyroidism of which a sensorineural hearing loss was demonstrated in only four patients. Heinemann (1968) claimed that only six patients out of a group of forty-two patients with various hypothyroid conditions had a sensorineural hearing loss. On the whole it appears that in acquired hypothyroidism the hearing disability appears in a far smaller percentage of patients than it does in congenital hypothyroidism.

The severity of the hearing impairment in acquired hypothyroidism does not seem to be as severe as in the congenital state (Ritter & Lawrence, 1960). Hearing impairment in acquired hypothyroidism is not explained by organic damage to the labyrinth. The inability to demonstrate a definite morphological correlation with the hearing impairment may be due to limitations of the histological method. De Vos (1963) reported that the organ of Corti was not found to be morphologically changed in animals in a state of acquired hypothyroidism. The only anatomical lesion found was a slight degeneration of the spiral ganglion. Experiments on animals with induced hypothyroidism showed no change in the sensory cells (Ritter, 1967). Kohonen et al. (1971) found minute morphological changes but considered them insufficient to explain the functional impairment. The lack of findings of lesions in the neural structures of the cochlea and yet the slight degeneration of the spiral ganglion noted by De Vos (1963), together with the information of a perceptive deafness in a certain percentage of the humans with hypothyroidism, brought De Vos to presume a nervous or a central involvement of the auditory system. Conversely, a precipitate of acid mucopolysaccharides was demonstrated in the scalae of cochleas from hypothyroid guinea pigs in recent histochemical observations (Shatzle & Haubrich, 1967). As most researchers did not find structural or morphological lesions that could explain the hearing loss, we thought that the subject would be elucidated by studying the difference in the function of the peripheral hearing mechanism in hypothyroidism. In this study we chose to compare cochlear action potentials aroused by unfiltered clicks before and after induced hypothyroidism.

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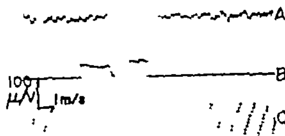


Fig. 2. Original recording. Acoustic evoked potentials by unfiltered clicks at 80 dB SPL. A = direct recording, B = average of 50 presentations, C = time scale.

(b) Unfiltered clicks from a home-made alternating positive–negative pulse generator.

(c) Filtered clicks obtained by passing unfiltered clicks through a narrow-band filter tuned to the desired central frequency (Madsen 20 1/3 octave filter set).

The intensity required was controlled by a home-made power amplifier and monitored by a permanently installed condensor microphone (Brüel & Kjaer type 4132) connected to a frequency analyzer that was used as a linear sound level meter (Brüel & Kjaer type 2105). The potentials from the animal were passed through a pre-amplifier and then amplified (Medelec AVM 6). The signal was then displayed and recorded by an ultraviolet beam (Medelec DFO 6 + T II). The unfiltered clicks form a square wave with a width of 0.1 msec at a rate of 10 pulses per second. The pulses are of alternating polarity.

In Fig. 2 is shown an example of the recording obtained with the instrumentation used in this study. The upper tracing is the direct recording from the electrode placed in the empty facial canal in the vicinity of the VIII nerve. The middle tracing shows the averaging of 50 presentations of unfiltered clicks at 80 dB sound pressure level. The number of presentations and the length of the recording which had to be averaged can be varied at will according to the needs and recording conditions. The lower tracing is the time scale. It can be moved so as to be superimposed on the upper or middle tracings, thus allowing a very accurate measurement of time-related phenomena.

Procedures

Complex problems arise in this sort of experiment where electrical measurements made over a few months are to be compared. The problem had to be resolved of implanting an electrode and keeping it in position without causing a tissue reaction that would alter the recording conditions, and furthermore to be both near the VIII nerve in order to get clear recordings, yet be far enough from the inner and middle ear structures so as not to cause operative or postoperative damage. We developed a novel technique described below which seemed to solve these problems.

The superior bulla is exposed using sedation with 10–12 mg Nembutal and local anaesthesia with Procaine. After opening the bulla one can see in the posterior part the protrusion made by the vertical and horizontal semicircular canals and in the anterior part, the blueish colour of the thin bony wall separating the bulla from the cavity of the middle ear (Fig. 3). Inferiorly the incudo-malleolar bone is easily

Material

Stainless steel electrodes were chronically implanted into the ear of 40 guinea pigs weighing between 250–300 grams From this group 4 animals were discarded because the recorded action potentials were weak and unstable The fact is explained by damaging of the insulation of the electrode during implantation These animals were used as a normal control group for blood tests Two animals developed post operative ear infection and had to be eliminated An additional 4 animals were used to check the range of variability of the recorded VIII nerve action potentials Measurements carried on over more than a month showed large variability in magnitude of the A P recorded from different animals but in the same animal the action potentials remained stable. In the remaining 30 guinea pigs used for further analysis hypothyroidism was induced. The animals were divided into three equal groups In the first group a state of hypothyroidism was induced by administering between 4–5 mCi per animal of radioiodine (I^{131}) intraperitoneally Control performed one month later failed to detect any remnant of radiation from the neck The second group underwent total thyroidectomy A state of hypothyroidism was provoked in the third group by a daily oral administration of 1–2 mg of propylthio-uracil

Instrumentation

The guinea pigs were put in a soundproof case inside a metal box with a mesh top (Fig. 1) The sound stimuli were delivered to the animal from a horn-type loudspeaker (Geloso horn loudspeaker) Three types of stimuli could be used

(a) Pure tones from a sine generator (Krohn Hite 5100 A function generator).

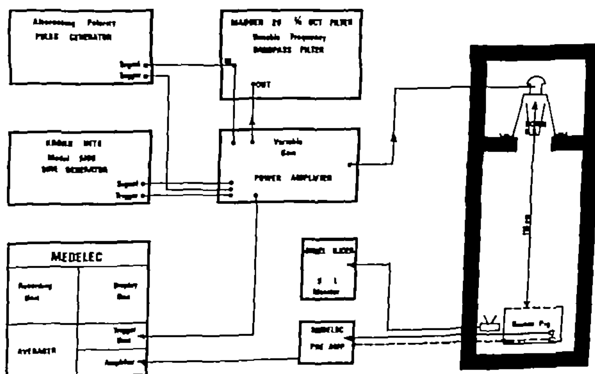


Fig 1 Set-up used for stimulation and recording of cochlear potentials.

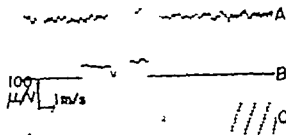


Fig. 2 Original recording. Acoustic evoked potentials by unfiltered clicks at 80 dB SPL. A = direct recording, B = average of 50 presentations, C = time scale.

(*b*) Unfiltered clicks from a home-made alternating positive–negative pulse generator

(*c*) Filtered clicks obtained by passing unfiltered clicks through a narrow-band filter tuned to the desired central frequency (Madsen 20 1/3 octave filter set)

The intensity required was controlled by a home-made power amplifier and monitored by a permanently installed condensor microphone (Brüel & Kjaer type 4132) connected to a frequency analyzer that was used as a linear sound level meter (Brüel & Kjaer type 2105) The potentials from the animal were passed through a pre-amplifier and then amplified (Medelec AVM 6). The signal was then displayed and recorded by an ultraviolet beam (Medelec DFO 6 + T II). The unfiltered clicks form a square wave with a width of 0 1 msec, at a rate of 10 pulses per second The pulses are of alternating polarity

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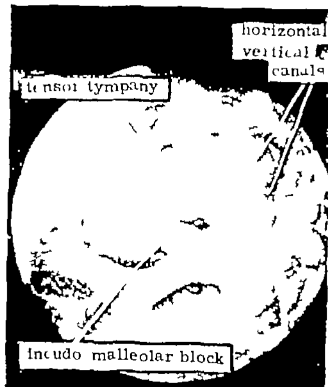


Fig 3 Exposure of superior bulla.



Fig 4 Opening of facial canal and section of the tendon of tensor tympanum muscle

recognized The ascending part of the facial canal passes through the denser bone between the semicircular canals and the blueish area

A small hole was drilled in the denser bone the nerve was exposed and cut (Fig 4) The tensor tympanum was visualized between the medial wall of the middle ear and the incudo-malleolar bone and severed (Fig 4) A specially made stainless steel electrode was introduced into the facial canal to a depth of 4.5 mm (Fig 5) The electrode was fixed in place with a drop of self-curing acryl The distal end of the electrode was brought through the skin in the occipital region and the wound was cleaned and sutured An inactive electrode made from uninsulated stainless steel was passed through the skin in the neck region

Immediately after the operation the action potentials aroused by unfiltered clicks of varying intensity were recorded Additional measurements were performed several days later If the recorded action potentials remained the same as after the operation the protruding part of the electrode was cut and the skin pinched in order to bury the electrode After approximately 2 months (considered sufficient to induce the hypothyroidism) the skin was



Fig 5 Positioning of the electrode in the facial canal

opened under local anaesthesia and light sedation with 6–8 mg Nembutal. The electrode was exposed and for several days new and repeated measurements were performed. No blood tests were performed during this period in order to confirm by laboratory findings the assumption that hypothyroidism was really achieved. In order to avoid artefacts connected with changes in the pulmonary ventilation due to anaesthesia, the sedation was the same during the various measurements and only just enough to keep the animal quiet. Several animals from each group were put on a replacement therapy of a daily oral administration of 1 mg of thyroidea sicca. The remaining animals were sacrificed and their blood analysed. At this time the middle ear was examined microscopically to make sure that no pathology had developed during the experimental period.

Results

Action potentials of 30 guinea pigs were compared with the potentials recorded before they became hypothyroid. All the guinea pigs showed changes following hypothyroidism in three main features: the magnitude, the shape and the delay time of the action potentials. Action potentials of a hypothyroid guinea pig that received radioiodine are illustrated in Fig. 6. Action potentials were recorded at varying acoustic intensities. A small change was seen in the shape and magnitude of the action potentials, especially at the lower intensities. At 6 weeks hypothyroidism was not yet fully induced. At 16 weeks there were marked changes in magnitude, shape and delay over the whole range of intensities.

The animal was put on replacement therapy for a period of 7 days to ascertain whether the changes in action potentials were due to the hypometabolic state. A swift recovery was obtained in the magnitude of the potentials, yet the shape of the potentials recorded did not match the original recordings. Blood tests performed 3 weeks after interruption of the replacement therapy showed PBI 0.7 µg % and T4 0.1. Action potentials measured before the animal was bled showed a disappearance of the improvement obtained during the replacement therapy.

Examples of action potentials obtained from 3 guinea pigs from the group that underwent total thyroidectomy are seen in Fig. 7. The action potentials aroused by a filtered click with a central frequency of 3.2 kHz at a S.P.L. of 80 dB are seen in the first column. Changes in the action potentials caused by hypothyroidism between 16 and 18 weeks are shown in the second column. The improvement obtained after 10 days of replacement therapy is demonstrated in the third column.

The changes during hypothyroidism caused by administration of propylthio-uracil for a period of 12 weeks on various acoustic stimuli are illustrated in Fig. 8. The changes in the action potentials aroused by unfiltered clicks and filtered clicks centered at 960 Hz, in one centered around 1.6 kHz, and one at 3.2 kHz, are shown. The intensity was 80 dB S.P.L. The delay time found in the recordings of the action potentials using the same intensity of sound stimuli during the hypometabolic state was increased by 0.3–0.6 msec.

Discussion

To extrapolate from the alteration of the action potentials in animal experiments to the hearing impairment observed in patients with hypothyroidism, is hazardous. The justification in doing so is that action potentials are the only signal conveyed to the brain and there

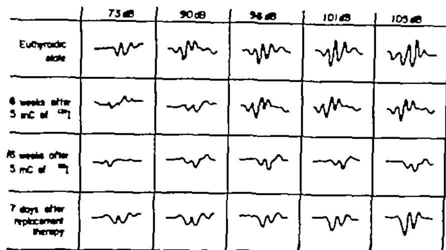


Fig 6 Graph obtained from the averaged responses of 50 presentations of unfiltered clicks In this animal the hypothyroidism was induces by 5 mCi of radioiodine The deterioration of the cochlear action potentials reached its maximum after 14–16 weeks and was more evident at lower intensity of sound stimuli.

fore they have to contain all the necessary information for the higher auditory centers to accurately process the acoustical message We conclude that a correlation exists between the diminished magnitude of the action potentials and the loss of hearing sensitivity found in hypothyroid patients This leads us to the suspicion that even hypothyroid patients having a normal threshold could have some disability in the supraliminal hearing which could be objectively demonstrated The change in the pattern of the signal could be related to some hearing disability in the hearing above the threshold

We believe that some hearing disability must exist above the threshold which is not detected by routine audiological methods The middle ear component as so frequently found accompanying the sensorineural hearing loss could have other explanations than the usual myxedematous changes in the middle ear An interference with normal propagation of sound waves through the cochlear scalae could have the same effect as in Menière s disease in which a mixed type of hearing loss is found without any middle ear pathology The observations made upon hypothyroid patients with a mixed hearing loss who unsuccessfully underwent regular treatment against a supposed pathology of the middle ear can be considered as proof Clinically it is well known that replacement therapy improves hearing but only

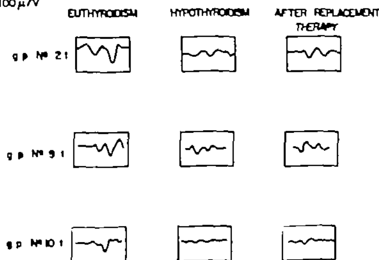


Fig 7 Hypothyroidism after surgical ablation of thyroid gland. Averaged action potentials evoked by 50 presentations of filtered clicks 1/3 octave and centered frequency 3 700 Hz at sound pressure level of 80 dB

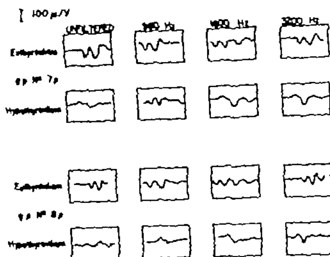


Fig. 8. Propylthio-uracil-induced hypothyroidism. Averaged action potentials evoked by 50 presentations of unfiltered clicks and 1/3 octave filtered clicks with different centered frequencies. Sound pressure level, 80 dB.

a few cases really reached the normal hearing level (Kohonen, Jauhiainen & Kaimio 1971).

In our study replacement therapy improved the magnitude of the action potentials, and in some cases it even reached the normal levels yet slight changes in the patterns of the action potentials remained. This leads us to the suspicion that even hypothyroid patients having a normal threshold could have some defect in the supraliminal hearing which could be objectively found by special auditory tests. The increased delay time of the action potentials found in our study could be correlated with the increased neural conduction time found in hypothyroid patients. A sluggish Achilles reflex is described in classical textbooks and recently an increased latency period in Auditory Evoked Response and unusual Békésy tracings due to hypothyroidism were found (Rubinstein, M. et al.).

Acquired hypothyroidism is believed to be far from uncommon, and aside from the clear-cut clinical cases many endocrinologists believe in the existence of sub-clinical forms. The results obtained in our study can easily be correlated with the clinical findings. Therefore it seems to us that more studies using this experimental model would be helpful. The information obtained could improve our knowledge concerning the specific pathology and contribute in establishing an early diagnosis in patients suffering from hypothyroidism.

Summary

Hypothyroidism was induced in guinea pigs by various methods. Using a new technique electrodes were permanently implanted and action potentials aroused by different sound stimuli recorded and measured. The results obtained before and during the hypometabolic state were analysed and compared with those obtained after replacement therapy. A tentative attempt was made to extrapolate the changes in pattern and magnitude of the action potentials caused by the experimentally induced hypothyroidism, to the hearing disorders observed in patients with thyroid deficiency.

Zusammenfassung

Hypothyroidism wurde im Meerschweinchen unter Verwendung verschiedener Methoden ausgelöst.

Eine neue Technik der ständigen Elektroden implantation ist gewählt worden wobei Aktionspotentiale verschiedener Geräusch stimuli gemessen und auf Tonband aufgenommen worden sind

Die Ergebnisse bevor und während hypometabolischer Zustände sind analysiert und mit denen nach einer Substitutionstherapie verglichen worden

Es wurde versucht die Änderungen in Muster und Grösse der Aktionspotentiale die durch den experimentell verursachten hypothyreotischen Zustand aufgetreten worden sind auf die verschiedene Hörstörungen welche hypothyreotische Patienten kennzeichnen zu extrapolieren

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Prof M Rubinstein
Otorh nolaryngology Dept
Cha m Sheba Medical Center
Ramat-Gan
I ael

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1 Einleitung

Der endemische Kretinismus im Zusammenhang mit Hör- und Sprachstörungen ist seit langem bekannt und hat immer wieder Diskussionen entfacht, inwieweit und ob überhaupt der Schilddrüse eine Bedeutung für die normale Entwicklung des Ohres zukommt. Ist es doch eine Tatsache, dass die Verbreitung der Gehörstörungen weder mit der Häufigkeit des endemischen Kretinismus noch mit der Intensität der Kropfendemie parallel geht (Trotter 1960, Greenwald 1960, Costa und Ferraris 1963). Erste Beschreibungen derartiger Krankheitsbilder gehen in frühe Zeitepochen zurück. So berichten römische Autoren über den Alpenkropf (Juvenal und Vitruv). Im 16. und 17. Jahrhundert weisen besonders Schweizer Ärzte wie Paracelsus und Felix Plater (1530–1619) auf den Kretinismus hin, wobei Plater als erster auf das Vorkommen von Taubstummheit „mit kropfiger und kretiner Degeneration" hinwies. In seinem 1656 in Basel erschienenen Buch „praxos medicae opus cum centuria posthuma emendatum et auct. a Felice Platero" erwähnt er eine Art von Taubheit, die in den Alpengegenden auftritt und durch Taubstummheit in Verbindung mit einem Kropf charakterisiert ist. Ätiologisch nimmt Plater an, dass die Erkrankung durch eine vom Kropf zum Ohr hin fliessende Flüssigkeit hervorgerufen wird. Er schreibt: „Sicuti *in alpinis regionibus, hac de causa multos difficilem* auditum ab ortu vel mox in aetatis progressu una cum strumis illis ob similem causam *familiariter* habere cernimus" (nach Politzer 1907).

Eingehende Untersuchungen zu diesem Problemkreis blieben Forschern im vorigen Jahrhundert vorbehalten – allen voran H. Bircher (1883), dessen Ausführungen zur endemischen Taubstummheit grundlegende Aspekte eröffnete. Die Untersuchungen wandten sich jetzt mikromorphologischen Methoden zu, was durch den weiteren Ausbau d… Othhistologie mit ihrer verfeinerten Techn… wesentlich erleichtert wurde. Siebenma… (1906), Oppikofer (1913), Schlittler (191… Brock (1920) und Nager (1921) stellten ke… krankhaften Veränderungen des periphe… Hörorgans fest und hielten als Ursache für … Sprach- und Gehörstörungen eine zentr… Schädigung für wahrscheinlich. Anderers… bestand für die damaligen Autoren kein Zw… fel, dass im peripheren Hörorgan beim … ausgebildeten Krankheitsbild des ende… schen Kretinismus typische morphologis… Veränderungen nachweisbar sein könn… Einmal Veränderungen im Mittelohr wie f… lende Pneumatisation des Warzenfortsat… mangelhaft angelegtes Antrum, Verengen… der Paukenhöhle, kleine Fensternisch… Verklumpungen von Gehörknöchelchen, V… dickung der Mittelohrschleimhaut, zum an… ren Alterationen des Innenohres, die jed… nur geringgradig ausgeprägt waren wie „a… phische Zustände der Hörzellen des C… organs und der Ganglienzellen", auch V… änderungen der Stria vascularis (Alexan… 1909, 1919), „eigentümliche Bildung des C… organs (hyaline, säulenförmige Leiste)" (S… benmann 1904, Schlittler 1917, Nager 19… Mayer 1919, Oppikofer 1921, Steu… 192… a, b).

Anlass zu vorliegender Studie war die Fi… *von Publikationen* mit mehr oder wenig… wahrscheinlichen morphologischen Befun… am Hörorgan schilddrüsengestörter Patien… sowie der experimentell weitgehend ungekl… te Einfluss des Schilddrüsenhormons auf … Feinstrukturen des Innenohres. Die *früher*… Untersuchungen beschränkten sich *f*… ausschliesslich auf Beschreibungen v… Krankheitsfällen des endemischen Kretin… mus und der im späteren Lebensalter erw… benen Hypothyreose mit konsekutiver H…